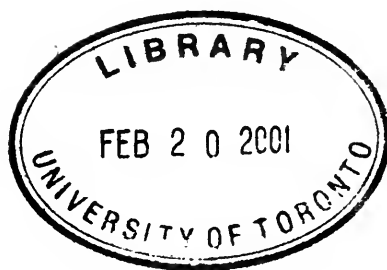




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THE  
AMERICAN  
JOURNAL OF PHARMACY

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PUBLISHED BY AUTHORITY OF THE

PHILADELPHIA COLLEGE OF PHARMACY

EDITED BY

HENRY KRAEMER

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# THE AMERICAN JOURNAL OF PHARMACY

JANUARY, 1914

## THE ASSAY OF MERCURIC CHLORID TABLETS.

BY ROBERT M. CHAPIN,

Bureau of Animal Industry, U. S. Department of Agriculture.

At the present time mercuric chlorid tablets, especially those prepared after the well-known Wilson formula, are very widely used, and are used moreover with implicit confidence in the accuracy of their declared content of mercuric chlorid under circumstances which render such accuracy a matter of considerable importance to individual welfare and to the public health in general. There can be no question of the desirability of assay methods which shall be fairly accurate, yet simple and rapid enough to be freely used by manufacturers, pharmacists, hospitals, and sanitary officials at a minimum of expense and chemical equipment.

Several years ago Rupp<sup>1</sup> proposed a rapid method for the determination of mercury in various compounds, involving the following steps: (1) Reduction to metallic mercury by formaldehyde in alkaline solution in presence of potassium iodid; (2) solution of the precipitated mercury in excess of standard iodine solution after acidification with acetic acid; and (3) titration of excess iodine by standard sodium thiosulphate. A modification of the method is now official in the German Pharmacopœia for the assay of tablets composed of mercuric and sodium chlorids.

In this country Smith<sup>2</sup> has thoroughly studied the Rupp method when applied to pure mercuric chlorid, obtaining, when certain modi-

<sup>1</sup> Rupp, E. Ueber die volumetrische Bestimmung des Quecksilbers. *Be-richte der Deutschen Chemischen Gesellschaft*, Vol. 39, No. 14, pp. 3702-3704. Berlin, Nov. 10, 1906.

<sup>2</sup> Smith, Carl E. Volumetric determination of mercury. *AMERICAN JOURNAL OF PHARMACY*, Vol. 83, No. 7, pp. 311-315. Phila., July, 1911.

fications were introduced, a recovery of 99.8 to 100.3 per cent. of the mercuric chlorid employed. Smith's modifications involved (1) the use of a larger amount of substance and reagents to reduce experimental errors, (2) a longer time of action by formaldehyde to insure complete reduction to metallic mercury, and (3) a much less degree of acidification before addition of iodine, since large amounts of free acetic acid tend to produce low results. Smith states that similarly good quantitative results were obtained when the method was applied to mixtures of mercuric chlorid and ammonium chlorid colored with aniline dyes. That is, the modified method is implied to be applicable to commercial tablets prepared after Wilson's formula (mercuric chlorid, 7.3 grains; ammonium chlorid, 7.7 grains; coloring matter, q.s.).

In this laboratory Smith's statements and results were confirmed on solutions of pure mercuric chlorid. Utter failure, however, followed attempts to apply his method either to commercial tablets or to similar laboratory mixtures of mercuric and ammonium chlorids. Abnormal precipitates appeared after addition of iodine, and results obtained were erratic and much too low. At the same time the method given in the German Pharmacopœia, slightly modified, was found to work smoothly and quantitatively.

The addition of formaldehyde to a solution of ammonium salts produces hexamethylenamin, which is known to form difficultly soluble compounds with both iodine and mercuric salts.<sup>3</sup> In Smith's modification, then, conditions appear to be such as to permit the formation and separation of hexamethylenamin compounds to the resultant vitiation of the process, while in the method of the German Pharmacopœia the greater dilution at which the process is worked either inhibits the formation of such interfering substances, or, more probably, is sufficient to retain them in solution and hence in a harmless condition. At all events, if, in addition to other minor modifications later to be noted, a volume of 75 c.c. of water is added at the time the contents of the flask are acidified before the addition of iodine, no abnormalities appear in the working of Smith's process, and the results are equally accurate in the presence or absence of ammonium chlorid.

Inasmuch as the method finally chosen here as most satisfactory is

Cohn, G. Die Verbindung des Urotropins. *Pharmazeutische Zentralhalle*, Vol. 52, No. 44, pp. 1173-1179. Dresden, Nov. 2, 1911.

somewhat different in details from either of the two modifications already noted, the points of difference and the reasons therefor will be discussed.

In the first place, while it is true that the use of large amounts of substance and reagents tends to reduce the relative magnitude of experimental errors, there is a point beyond which any slight possible gain in accuracy is attained only at the sacrifice of an unwarranted measure of simplicity, convenience, and rapidity. It is certainly open to question whether this point is not passed by Smith's modification with its considerable consumption of standardized solutions, especially when the total volume of liquid worked with is increased by the 75 c.c. of water here found necessary to prevent interference by hexamethylenamin compounds. The writer therefore recommends the employment of 0.20 to 0.25 gram of mercuric chlorid for each test, and the addition of 25 c.c. of tenth-normal iodine.

*Experiment 1.*—To test the limits within which the results of parallel determinations may fall if the above proportions are used, a series of seven parallel tests were made on a solution of commercial tablets, using the equivalent of one-half tablet for each test. Aside from the use of volumetric apparatus which had passed the requirements of the Bureau of Standards, no precautions not employed in ordinary quantitative work in any laboratory were observed. The cubic centimetres of iodine solution (tenth-normal  $\times$  0.978) consumed in the solution of mercury were as follows: (1) 17.72; (2) 17.73; (3) 17.68; (4) 17.69; (5) 17.72; (6) 17.73; (7) 17.65; an extreme difference of 0.08 c.c. The average weight of mercuric chlorid per tablet was therefore found to be from 0.4677 to 0.4698, a difference of 0.45 per cent. The range of variation reported by Smith in a series of five tests by his method on pure mercuric chlorid was 0.5 per cent.

Secondly, the proportion of potassium iodide should be considerably increased over that employed by either Rupp or Smith in order to avoid the formation of mercurammonium compounds which result when caustic alkali in excess is added to a solution containing potassium mercuric iodide and ammonium salts, as in the well-known "Nessler test."

Thirdly, the presence of ammonium salts in one way or another operates to retard the reduction to metallic mercury so that it is not complete in 5 minutes though apparently so after 10 minutes.

Lastly, commercial formaldehyde solutions often contain foreign substances, some of which conceivably may consume iodine, and in fact such solutions have here been found which did possess this

power in slight but distinct degree. Hence a standard thiosulphate solution should be made the basal standard against which the iodine solution is standardized by running a blank assay with the other solutions and reagents intended for actual use.

The method finally chosen for tablets after Wilson's formula is as follows: Weigh 5 tablets, dissolve in water, dilute to 100 c.c., and pass through a dry filter, discarding the first 20 c.c. of filtrate. From the remainder pipette 10 c.c. (equivalent to one-half tablet) into a glass-stoppered 250 c.c. Erlenmeyer flask, add  $2\frac{1}{2}$  grams pure powdered potassium iodide, mix to entirely dissolve, and then wash down the sides of the flask with 20 c.c. of normal caustic alkali. Add exactly 3 c.c. of 37 per cent. formaldehyde solution, mix thoroughly, and let stand for at least ten minutes, swirling the flask occasionally. Then wash down the sides of the flask with a mixture of 5 c.c. of 36 per cent. acetic acid with 25 c.c. water; mix, and without delay run in from a burette 25 c.c. of tenth-normal iodine while constantly swirling the flask. Stopper the flask tightly, shake vigorously for three minutes, then after giving the contents a final swirling motion leave at rest for two minutes. If then no undissolved mercury can be detected at the bottom the stopper is removed, rinsed, together with the neck of the flask, with a stream from a wash-bottle, and the excess iodine titrated with tenth-normal sodium thiosulphate, adding starch solution only when the iodine is nearly consumed.

Standardize the iodine solution by running a blank assay on 10 c.c. distilled water.

Subtract the volume of thiosulphate solution used in the assay from that used in the blank. The difference multiplied by the factor 0.0271 for strictly tenth-normal sodium thiosulphate will give the average weight of mercuric chlorid per tablet. For a direct check upon the value of the sodium thiosulphate solution run an assay on 10 c.c. of a  $2\frac{1}{2}$  per cent. solution of mercuric chlorid of known purity.

While mercuric chlorid is the important active ingredient of tablets made according to Wilson's formula, nevertheless ammonium chlorid is an essential part of the formula, added in order to render the tablets easily soluble and to inhibit the formation of insoluble, and hence inactive, compounds of mercury. An assay of such tablets

ought therefor to include an estimation of ammonium chlorid, especially when a simple and convenient method is available.

The method for ammonium chlorid here adopted is an adaptation of the process of Ronchèse,<sup>4</sup> which is based on the reaction between formaldehyde and a neutral ammonium salt, whereby methylenamin,  $(\text{CH}_2)_6\text{N}_4$ , is formed, the acid originally contained in the ammonium salt being released and becoming titratable with standard caustic alkali and phenolphthalein. The strengths of reagents, etc., recommended by Wilkie<sup>5</sup> have been adopted.

Titration by standard alkali and phenolphthalein can not of course be conducted in presence of mercuric chlorid. This difficulty, however, is easily overcome by throwing the mercury into a complex ion through the addition of potassium iodid. The method is as follows: Into each of two 150 c.c. Erlenmeyer flasks pipette 5 c.c. (one-fourth tablet) of the tablet solution previously prepared for the estimation of mercuric chlorid (5 tablets per 100 c.c.) and add to each flask 2 c.c. of a 20 per cent. solution of potassium iodid.

Dilute one volume of 37 per cent. formaldehyde solution with three volumes of water, measure 20 c.c. of the mixture into a small flask, add 0.5 c.c. of phenolphthalein indicator solution, neutralize with tenth-normal barium hydrate or caustic alkali, then flow the solution over the sides of one of the flasks (flask A) containing tablet solution, and mix well. To the other flask (flask B) containing tablet solution add about 65 c.c. water.

Now add to flask A 25 c.c. water and titrate with tenth-normal barium hydrate or tenth-normal caustic alkali free from carbon dioxid until, by using flask B as a standard for comparison, a color change is perceptible (titration A).

Add methyl red to flask B and titrate with either tenth-normal acid or alkali as needed (titration B).

To titration A add titration B if performed with acid, or subtract if performed with alkali. The resultant figure multiplied by the factor 0.0214 for strictly tenth-normal alkali will give the average weight of ammonium chlorid per tablet.

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<sup>4</sup> Ronchèse, A. Nouveau procédé de dosage de l'ammoniaque. *Journ. de Pharmacie et de Chimie*, Vol. 25, No. 12, pp. 611-617. Paris, June 16, 1907.

<sup>5</sup> Wilkie, John M. The Ronchèse method of determining ammonia and its extension to the determination of the total acid content of organic ammonium salts and ammoniacal solutions. *Journal of the Society of Chemical Industry*, Vol. 29, No. 1, pp. 6-7. London, Jan. 15, 1910.

For a direct check upon the value of the tenth-normal alkali run an assay upon 5 c.c. of a  $2\frac{1}{2}$  per cent. solution of pure ammonium chlorid.

Solutions, reagents, and water used should be free from carbon dioxid.

Ordinarily titration B is very small, sometimes zero, but usually calling for the addition of a few drops of tenth-normal acid.

As respects the end points with the indicators it is only possible to state that up to the present time no blue or green tablets which have been received by the writer have presented the slightest difficulty. The characteristic colors of the indicators of course do not appear in the presence of other coloring matter, but the change of tint, if standards of comparison are used, is delicate and distinct. No red tablets have been received for examination.

The reliability of the method may be shown by noting a few results.

*Experiment 2.*—Four tests made on 5 c.c. of a solution of 2 grams each of commercial C.P. chlorids of mercury and ammonium per 100 c.c. gave the following figures for titration A (titration B = 0), made with barium hydrate solution (tenth-normal  $\times 1.021$ ) which had been standardized against a laboratory stock solution of half-normal hydrochloric acid: (1) 18.24 c.c.; (2) 18.26 c.c.; (3) 18.29 c.c.; (4) 18.26 c.c.; an extreme difference of 0.05 c.c. and a recovery of 99.6 to 99.9 per cent. of the ammonium chlorid employed.

*Experiment 3.*—Three titrations made on 5 c.c. of the solution of commercial tablets employed in Experiment 1 gave titration B as zero, and titration A as (1) 22.64 c.c.; (2) 22.58 c.c.; (3) 22.62 c.c.; an extreme difference of 0.06 c.c.

It appears, therefore, that assay methods are now available for accurately and conveniently estimating mercuric and ammonium chlorid in commercial tablets. Knowing the weight of tablets taken to prepare the stock solution for assay, estimation of coloring matter and "filler" is merely a matter of subtraction. Further possible tests, such as degree of solubility, amount of insoluble matter, and uniformity of weight of individual tablets, are a matter of discretion with the analyst and need no discussion.



# SEASONAL VARIATIONS IN THE RESISTANCE OF GUINEA PIGS TO POISONING BY OUABAIN AND BY LIQUID PREPARATIONS OF DIGITALIS.

BY C. C. HASKELL, A.B., M.D.

In a previous paper <sup>1</sup> it has been shown that guinea pigs are more resistant to poisoning by ouabain during certain months of the year than at others. These results were confirmed in a general way by Vanderkleed and Pittenger <sup>2</sup> in a subsequent publication. It is of interest to compare the results secured in this laboratory with those reported by Vanderkleed and Pittenger.

I have used male pigs exclusively, and have been compelled to employ animals differing largely in weight; the majority, however, weighed 250 grams or more, so it seems best to compare my results with those obtained by Vanderkleed and Pittenger using "large males." In order to facilitate comparison, the average minimum lethal dose has been expressed in fractions of a gram per gram body weight and put in the following tabular form:

TABLE I.

Month.	Vanderkleed and Pittenger.	Haskell.
January.....1912	.00000025	.00000052 +
February.....1912	.00000030	.00000037
March.....1912	.00000032	.00000036
April.....1912	.00000033	.00000040
May.....1912	.00000033	.00000045
June.....1912	.00000033	.00000040
July.....1911	.00000021	.....
August.....1911	.00000021	.00000029
September.....1911	.00000021	.00000030
October.....1911	.00000021	.00000036
November.....1911	.00000024	.00000052
December.....1911	.00000028	.00000052

It is readily seen that the same general conclusion is deducible from both series of tests: the resistance of the pigs is least during the hot summer months and greatest in the cooler weather. In August, there is a difference of 38 per cent. between the lethal dose required

<sup>1</sup> AM. JOUR. PHARM., Vol. 84, No. 6, p. 241, 1912.

<sup>2</sup> *Jour. Am. Ph. Assoc.*, Vol 11, No. 5, p. 558, 1913.

in Indianapolis and that determined in Philadelphia; and in January, the enormous preponderance of 108 per cent. is shown by the Indianapolis lethal dose. Obviously, it is scarcely to be expected that we should secure very closely comparable results in assaying a galenical if such divergence occurs in testing a "pure principle."

In endeavoring to account for this disagreement, the technic employed should be closely scrutinized. It is a well-recognized fact that testing digitalis upon frogs requires the closest attention to details and necessitates the avoidance of any disturbing factors such as large variations in the weight of the animals and, especially, extremes of temperature. From previous statements of those who have employed the guinea pig method, one is led to infer that such extreme caution is not necessary when this method is used, and the results of Vanderkleed and Pittenger seem to show that weight and age are factors of little moment.

In all of my experiments, a solution of ouabain, 1 to 10,000 in 25 per cent. alcohol, was used. Vanderkleed and Pittenger do not state whether alcohol was present in the solutions they employed, but its absence would explain the smaller dose determined by them as compared to the dose I found necessary in August, because alcohol exerts a similar antagonistic action toward the absorption of subcutaneously-administered ouabain as it does toward digitalis administered in this way. Some other explanation, however, is necessary to account for the difference between the minimum lethal dose determined in Indianapolis in January (.00000052+) and that determined in Philadelphia for the same month (.00000025). The pigs used by Vanderkleed and Pittenger were kept in fairly warm quarters; while our animals were subjected to considerable variations in temperature, the thermometer occasionally registering as low as 50° F. This, I believe, has an important bearing on the resistance of the guinea pigs and, together with the influence of the alcohol used in my experiments, may serve to explain the difference in the lethal dose as determined in the winter months.

Since this earlier report, the minimum lethal dose of ouabain in 25 per cent. alcohol has been determined upon guinea pigs in a number of different months and a comparison is of some interest. In Table II such a comparison is given.

These figures indicate that the temperature influences the powers of resistance. During the extremely cold winter of 1911-12 the

dose for November, December, and January was .00000052: while during the much milder winter of 1912-13, the lethal dose was smaller. Where comparison is possible in other months, the difference never amounts to more than 15 per cent.

TABLE II.

Month.	1911.	1912.	1913.
January.....	.....	.00000052 +	.00000040
February.....	.....	.00000037	.00000042
March.....	.....	.00000036	.....
April.....	.....	.00000040	.00000037
May.....	.....	.00000045	.00000045
June.....	.....	.00000040	.....
July.....	.....	.....	.00000025
August.....	.00000029	.....	.00000025
September.....	.00000030	.00000036	.....
October.....	.00000036	.00000042	.....
November.....	.00000052	.00000040	.....
December.....	.00000052	.00000045	.....

Seasonal variations in the resistance of test animals may be obviated by the use of a satisfactory standard, and Vanderkleed and Pittenger suggest the use of ouabain when galenicals of the "heart tonic" group are tested upon guinea pigs. The use of ouabain is justified, however, only when it has been shown that the variations in the resistance toward poisoning by ouabain parallels that toward poisoning by the galenicals under consideration. Opportunity has occurred to determine the minimum lethal dose of a small number of samples of tincture and fluid extract of digitalis at different seasons of the year. Some of the tinctures were made by the U.S.P. method and some were made with a menstruum containing 75 per cent. alcohol. All of the fluid extracts were made with a menstruum containing 70 per cent. or 80 per cent. alcohol.

In testing the tinctures, portions were evaporated to a semi-solid consistence upon the water-bath and the residue suspended in an amount of distilled water equal to the original volume of the portion taken for evaporation. The same procedure was followed with the fluid extracts, save that the volume of distilled water was five times that of the fluid extract taken. For reasons that will be apparent later; it is desirable that the preparations be divided into two groups; one comprising preparations containing about 50 per

cent. alcohol; the other comprising those containing from 70 to 80 per cent. alcohol.

The comparison of the lethal doses for two tinctures made with 50 per cent. alcohol and the lethal dose for ouabain during the same months is given in Table III.

TABLE III.

	June, 1912.	Oct., 1912.	Dec., 1912.	Jan., 1913.	Aug., 1913.
Ouabain.....	.0000004	.00000042	.00000045	.0000004	.00000025
Tr. Digitalis U. S. P. 434900.....	.004	.004	.007+	.0065	.0042
Tr. Digitalis U. S. P. 457579.....	.....	.....	.0075	.....	.0052

So far as can be judged by this limited number of experiments, "seasonal" variations in the resistance of guinea pigs toward poisoning by ouabain and by tinctures of digitalis made with 50 per cent. alcohol follow the same general curve. In January, 1913, the lethal dose for Tincture 434900 was .0065, while in July, 1913, it showed a decrease of 35.4 per cent.: the lethal dose of ouabain showed a decrease of 37.5 per cent. during the same time. In December, 1912, the dose of Tincture 457579 was .0075, while in July, 1913, it was 30.6 per cent. less: the dose of ouabain suffered a decrease of 44 per cent.

In testing the preparations containing relatively high percentages of alcohol, entirely different results were obtained. These are so surprising that it was only after confirming them repeatedly that I could feel that they were not due to some error in testing. The tests were carried out in a manner exactly similar to those dealing with the tinctures just discussed and the difference in the behavior seems to depend upon an essential difference in the composition of preparations made with 50 and 75 per cent. alcohol respectively.

From these results, it is evident that no seasonal variation has been observed in the resistance of guinea pigs to poisoning by fluid preparations of digitalis made by percolation of the leaf with menstrua containing 70 to 80 per cent. alcohol. Tinctures made with 75 per cent. alcohol differ in several important points from those made with 50 per cent. alcohol, but it seems almost incredible that the resistance of guinea pigs to poisoning by the two should follow

TABLE IV.

	Ouabain <sup>1</sup>	Tr. Digitalis 471124	Tr. Digitalis 461011	Tr. Digitalis 467056	Tr. Digitalis <sup>2</sup> 24678	F. E. Digitalis 461015	F. E. Digitalis 1654092
Jan. 1912	52						
1913	40	.....		.0024	.0025		
Feb. 1912	37						
1913	42						
Mar. 1912	36	.....			.0025		
1913	.....	.0027					
Apr. 1912	40	.....			.0030		
1913	37						
May 1912	45						
1913	45						
June 1912	40						
1913							
July 1912							
1913	25	.....			.0025	.00022	.00047
Aug. 1912	29						
1913	25	.0025	.0020	.0023			
Sept. 1912	36						
1913							
Oct. 1912	42	.....			.0025		
1913							
Nov. 1912	40	.....			.0025	.00023	.00032
1913							
Dec. 1912	45	.....	.0022				
1913							

<sup>1</sup> The figures in this column represent fractions of a gram to the eighth decimal (.00000052).

<sup>2</sup> Alcohol not removed from this tincture.

such different lines. A confirmation of these observations would certainly suggest that careful pharmacological study of digitalis preparations made with different menstrua would not entail a waste of time.

From the Laboratory of Experimental Medicine, ELI LILLY AND COMPANY, Indianapolis, Aug. 26, 1913.

## MAGMA BISMUTHI.

BY S. BERTHA MÜLLER, P.D.,

Assistant Pharmacist at the German Hospital, Philadelphia.

In recent years Magma Bismuth has become quite popular, so much so that it was deemed advisable to make the preparation official.

With that end in view several formulas have been proposed and duly tried out, but in our experience have not proved generally satisfactory.

The formulas proposed direct ammonia water to be used to precipitate the bismuth nitrate. This, in our experience, leads to considerable trouble trying to wash the resulting Magma free from the excess of ammonia. It takes a great deal of water to do so and even if one has succeeded in getting the final washings to no longer react with phenolphthalein the Magma itself will always give a strong reaction. To reduce the amount of ammonia water leads to a reaction in the opposite direction, giving a decided acid reaction which causes the gradual solution of the bismuth hydroxide. Furthermore, when the Magma is poured on a strainer for the purpose of washing it, the surface of the Magma very soon develops a metallic coating which certainly points to a decomposition going on and may be due to exposure to air. Unfortunately this is the only way the Magma can be washed because distilled water has the property of causing the Magma to curdle into large flaky masses, taking up considerable water and holding it so that it is utterly impossible to get the Magma to settle in order to wash it by decantation, thus preventing undue exposure to air.

Attention should also be drawn to the fact that the amount of bismuth subnitrate used, results in too thick a Magma. Furthermore, 80 grams of bismuth subnitrate cannot be satisfactorily dissolved in 60 c.c. of nitric acid. It takes 1 c.c. of nitric acid for every gram of bismuth subnitrate to be dissolved.

However, with some modifications the proposed official formula will give satisfactory results. In the first place the amount of bismuth should be somewhat reduced, then ammonium carbonate should be substituted for ammonia water, and lastly, distilled water containing 1-1000 sodium chloride should be used. By using ammonium carbonate the resulting Magma is not nearly so alkaline, it will not react with phenolphthalein but will and should react alkaline toward methyl orange. It therefore does not require nearly so much washing. It only needs to be washed until it is practically tasteless. The use of this small amount of sodium chloride in distilled water prevents the curdling of the Magma, and it therefore can readily be washed by decantation, no strainer being required. After sufficient washing it is allowed to settle to the required volume, which usually takes about a week.

Spigot water can also be used in place of distilled water if it has been previously boiled with 1 per cent. magnesium carbonate for

about 15 minutes, then cooled and filtered and 1-1000 sodium chloride added.

The following formula has been fairly satisfactory:

Bismuth Subnitrate .....	50.0
Nitric Acid .....	50.0
Ammonium Carbonate .....	80.0
Distilled water to make.....	1000.0

Dilute the nitric acid with an equal volume of water and dissolve the bismuth subnitrate in it, dilute further to 300 c.c. and filter through cotton.

Dissolve the ammonium carbonate in 3000 c.c. distilled water containing 1-1000 sodium chloride and filter.

Pour the acid solution slowly and with constant stirring into the alkaline solution. When the resulting precipitate has subsided, decant the supernatant liquor and wash by decantation until the Magma is practically tasteless, using distilled water containing 1-1000 sodium chloride. Then allow to settle to 1000 c.c.

When tested the Magma should react alkaline toward methyl orange.

## BOOKS AS A SOURCE OF DISEASE.

BY WILLIAM R. REINICK.

I do not for a moment want anyone to think that I am endeavoring to prove that books, as fomites, are so dangerous that they should be shunned like the plague, but simply to show that books, especially when greasy or moist fingers are placed upon the pages and covers, are excellent hiding grounds for bacteria, both pathogenic and non-pathogenic, and that the same care should be used as in handling other objects of like character.

### IS SUCH TRANSMISSION POSSIBLE?

As far as our exact knowledge of books and papers as a source of danger is concerned, we, at the present time, have very little evidence, but what we have proves beyond question, that disease may be contracted by this means. On the other hand there are many reputable physicians who claim that transmission by this means is an impossibility, due to the fact that the organisms could not exist

for any length of time under such adverse conditions. A statement of this character is generally made by one who only has a superficial knowledge of the subject, especially in its biological aspect. The apparatus needed to properly conduct experiments upon bacteria is quite expensive, and generally, the young physician who has just graduated has the time and possesses the enthusiasm to undertake these researches, but not the capital, and then when he has the means, he has so many patients that he cannot spare the time.

Another trouble is the extreme difficulty which arises when one is prepared to study this subject. On account of the great surface covered by the pages of the books, it means a long and tedious series of experiments, and even then, on account of their being invisible to the eye, one is not sure that he has obtained every speck of life that may be on the paper.

The knowledge that we are now acquiring as to the great resistance of these small forms of life to adverse conditions of climate and atmosphere, their resistance to degrees of heat, their wonderful adaptability to rapid changes of environment, food, and their power to remain dormant for a period more or less unknown at the present day, their ability to form a protective coat, which prevents penetration when placed in material that would otherwise destroy them, all these points indicate that we may be on the wrong track in using the present means of eradication. And furthermore, in making our laboratory tests we are forced to isolate the colonies, giving conditions foreign to their natural state of existence, and also the difficulty in separating them into distinct species.

Newman states as follows: "A word may be said here respecting the much-discussed question of species of Bacteria. A species may be defined as 'a group of individuals,' which, however many characters they share with other individuals, agree in presenting one or more characters of a peculiar and hereditary kind with some certain degree of distinctness. Now, as regards bacteria, there is no doubt that separate species occur and tend to remain as separate species. It is true, there are many variations, due in large measure to the medium in which the organisms are growing—variations of age, adaptation, nutrition, etc.—yet the different species tend to remain distinct. Involution forms occur frequently, and degeneration invariably modifies the normal appearance. But because of the occurrence of these, morphological and even pathological differences of environment and physical conditions must have marked effect



upon such sensitive units of protoplasm as bacteria; it has recently been proven that one great reason why modification occurs in pure artificial culture is that the species has been isolated from amongst its colleagues and doomed to a separate existence. One of the most abstruse problems in the immediate future of the science of bacteriology is to learn what intrinsic characters there are in species or individuals which act as a basis for the association of organisms for a specific purpose. Some bacteria appear to be unable to perform their regular function without the aid of others. An example of such association is well illustrated in the case of tetanus, for it has been shown that if the bacilli and spores of tetanus alone obtain entrance to a wound, the disease may not follow the same course as when with the specific organism of lactic acid bacilli, or the common organisms of suppuration or putrefaction also gain entrance. Again, the virulence of other bacteria is also increased by means of association. The bacilli coli is an example, for, in conjunction with other organisms, this bacilli, although normally present in health in the alimentary canal, is able to set up acute intestinal irritation, and various changes in the body of an inflammatory nature."

Among the higher forms of life we have, in a few hundred of years, recognized natural changes, or often brought the change about by artificial selection. Now if a change, quite noticeable, can be made during a period of years, in forms which do not produce more than one or two generations a year, what changes are able to take place, in forms capable of producing a new generation every twenty or thirty minutes, and these changes invisible to us?

Another source of failure to obtain positive results is due to the fact that conclusions are generally arrived at from twenty-four hour tests; and, if there is no result within that period, the experiment is marked negative and the material destroyed.

Very little information of value, to help in deciding whether or not books act as carriers, was received from the various Boards of Health of the United States. A circular letter requesting a list of cases, the source of which was traced to books and papers, was sent to the Boards of Health of each State and forty-one cities. Answers were received from only ten States and nineteen cities, about 30 per cent. of the total number of letters sent.

With these replies no cases were given, although some of the officials stated it to be their belief that diseases were contracted through contact with books, while others ridiculed such a possibility.

Quite a number of physicians have sent me histories of cases, which they have observed during their practice.

The medical and library periodicals are constantly printing notices about disease being contracted from books, and as in the case of the theory of insects transmitting disease germs, at first ridiculed, but now acknowledged to be true by the most skeptical, so are books now passing through the same criticism.

#### DISEASES CLAIMED TO HAVE BEEN TRACED TO BOOKS.

*Scarlet Fever.*—Dr. J. Allen Palmer, of Erie, Kansas, notes a case of scarlatina developing in a girl, living in a town where there had been no cases of the disease for months, nor had she been exposed to personal contact. Investigation showed that the patient had received a letter a few days previous to the appearance of the rash, from a child living some sixty miles from her, who was just recovering from scarlatina. Another case of transmission was traced by Dr. Howard W. Lyon, of Chicago. In this instance a little girl living in Chicago contracted scarlatina from being allowed to handle a letter just received from a home in Minneapolis, where one of the family had the disease.

Dr. A. Maverick, of San Antonio, Texas, sent the following case: A boy convalescent from scarlet fever read a book from the public library and used as book-marks strips of skin peeled from his hands and feet. Unknown to the physician, the book was returned to the library by a servant of the household with no attempt at sterilization or even removing the pieces of skin. During the next month, two boys in different families who borrowed the book from the library, caught scarlet fever and one died from the disease.

*Diphtheria.*—Dr. Robert Britton, of Downsville, New York, writes of two cases in 1902, one of the patients dying, and as there were no cases of the disease in the neighborhood, the question arose where had the children contracted the infection. Questioning revealed, that on account of the weather and conditions of the road they did not attend school on March 27, but played in a house having a garret, in which were stored some old school books which had been taken from an old farm-house on this farm—in which in 1860 had occurred six cases of diphtheria, four of which were fatal in forty-eight hours.

*Small-pox.*—Small-pox is one of the most contagious diseases, and few who are exposed escape infection. The contagion exists in

the pustules, in the fluid of the body, and apparently in the exhalation from the lungs and skin. The dried scales thrown off during desquamation are the most important element in disseminating the malady, and is often communicated, through the medium of clothes, furniture, books, etc., which have come in contact with patients.

Dr. P. A. Jordan, of San Jose, California, states the following: A man, a great reader, continuously used books from a circulating library located in a neighboring town in which there was an epidemic of small-pox, and later developed a severe form of small-pox.

*Blood-Poisoning.*—Dr. Emericus Karacson, while making a translation of a Turkish Manuscript, in one of the Mosques in Turkey, had his fingers soiled with some of the mould which covered the old musty tomes, and accidentally touched a cut on his face; a few weeks later his face swelled up, causing him intense pain. A quick operation relieved him of this and his face regained its normal size, and he soon resumed his work, apparently in perfect health. About a month later he was taken ill with fever and treated first for influenza, then for typhoid fever. His condition growing worse, a Hungarian physician was sent for, who diagnosed the case at once as blood-poisoning, caused no doubt by the fungi that had entered the patient's system through the abrasion on the face, and he died within a few days.

*Veneral Diseases.*—That the danger to man from what are called the "social evil" diseases, after exacting a cost in human life and physical disability beyond computation, and the necessity of using means which will prevent its spread, is now recognized, as seen by the numerous societies being formed to furnish speakers and publish literature upon the subject, thus forcing the public to face the question as it has never been done before.

A list of articles found to be carriers of the germs of gonorrhea, the one most likely to be contracted through contact, would include every article of domestic and public use, and even the hands of the unclean and ignorant may transfer the germs to the articles. A number of cases have been traced to books.

Diseases, besides these mentioned, have been named as being transmitted by books, and there is no reason to doubt that the germs of other diseases found on fomites will also be found on books. The bacillus of anthrax, which occurs in cattle, must certainly be found on the leather bindings, as it is frequently transmitted through

abrasions of the hands in cases of those who have the occasion to handle infected wools and hides.

*Tuberculosis.*—The number of bacilli in the sputum of a person suffering from tuberculosis is enormous. Nuttall estimated that a person moderately advanced in the disease, expectorated between two and four billions of bacilli every twenty-four hours. One having this disease does not at once become helpless, and in the meantime the patient generally spends a great deal of his spare time reading, and as this disease usually causes the one afflicted to cough a great deal, often involuntarily, it is but natural that particles of the sputum will be caught on the paper of the books, ready to be transmitted to another victim.

*Dust.*—I do not think that enough study has been given to the bacteria found in dust, as far as public institutions are concerned. Careful consideration of the examinations already made of dust from various sources, especially in the industrial trades during the past few years, will show at once that the health is often affected by the impurities found in the air inhaled, and that the purifying of this air is of greatest importance from a sanitary standpoint. Besides the danger from exposure to the so-called diseases, the germs of which are stated to be borne in the air, the pollution of the air by organic and inorganic dust is beyond a doubt the cause of a great deal of ill-health, and death.

An analysis made by Prof. Charles H. Lawall of dust collected by me at the State Library of Florida, at Tallahassee, off of books that had not been disturbed for many years, gave the following result:

“Ash (inorganic material, mainly sand), 54.90 per cent.

“Organic matter consists of much unidentifiable matter, in which, however, could be distinguished microscopically the following: wood fragments, cotton, linen, silk, wool (some of them dyed bright colors), hairs of various kinds, both plant and animal, starch grains, spore and an occasional yeast cell. No evidence was found of arsenic or mercury or other poisonous metals or their compounds, except what might be called a faint trace of arsenic, which was traced by a method so delicate as to detect arsenic in almost any substance from which it has not been specifically removed.”

Dr. McFadden and Mr. Lunt seem to prove the paucity of bacteria in very dusty air. The evidence otherwise available is entirely conclusive that the risk to disease infection is much greater indoors than out in the open, where the germs are exposed to the

sunlight, which is a great factor in keeping the germs in an inactive state.

But, besides the danger of infection from inhaling disease germs found in the dust, there is also to be considered that it is the cutting edges of the particles of dust, which when inhaled scratch or cut the delicate air passages leading to the lungs and also the lungs themselves. The finer dust will not, perhaps, act as quickly as the coarser grains, but it means that the evil result will take a much longer time before making its appearance.

It is known that those who spend most of their time in outdoor occupations, generally have better health than those who are compelled to work in factories, offices, etc., and the first thought of sanitary science to-day is the elimination of dust.

It is extremely difficult, in fact almost impossible, to trace many cases of infection on account of the long period between the first infection and the appearance of the disease in a form to demand medical attention.

Dr. Hugh H. Brown, of Washington, D. C., and an assistant, in 1907, moved a large number of books which had not been disturbed for quite some time. Within a few days both contracted severe colds, characterized by distinct bubbling, and a severe cough accompanied by a feeling of compression and pain in the chest, and an exceedingly profuse and purulent expectoration of a deep yellow color the consistency of thick cream. The cold lasted about two weeks.

*Vitality of Bacteria.*—Before considering the mode of overcoming these organisms, consideration should first be given to their power of resistance to disinfection, sterilization, etc.

Bacteria exist in nature in three states:

(1) As adult or fully-developed and active microorganisms, with all the characteristics of parasites.

(2) As spores or reproductive cells endowed with latent life.

(3) As desiccated germs, whose vital principle had been suspended but not destroyed; which, when placed in a moist and suitable environment, possess the power of resuscitation.

"The air germs," says Professor Tyndall, "differ much among themselves in their tendency to development; there are some which are young and there are others which are old, some dry and some wet. The same water infected by those germs requires more or less time to develop bacterial activity. This explains the difference in the rapidity with which epidemic diseases act upon different persons.

In certain cases the period of incubation, if it can be so called, is long, in others it is short; the difference is the result of the different degrees of preparedness of the contagious matter, and I personally believe that the health of the person infected has most to do with the appearance or non-appearance of a disease."

The length of time that the different pathogenic bacteria can withstand drying varies greatly. Krausz placed bacteria from 48-hour old cultures in books and kept them in the dark at room temperature. He found that cholera lived only 40-95 days and tubercle bacilli 80-103 days. Other investigations confirm his results except in the cases of tuberculosis and diphtheria. Abel found that diphtheria bacilli retained their virulency on toys for six months and this is the length of time that Von Scham gives. Lion and Von Schab both say that tubercle bacilli withstand drying from six to nine months.

The number of bacteria that may be found on much-used books was investigated by Lion. A novel from a public library varied from 250 bacteria per 100 square centimetres on the middle of a clean page to 1,250, 1,875, and 3,350 on the dirty edges. A college atlas showed from 650 to 1,075 per 100 square centimetres; an anatomy book 2,275 to 3,700. The bindings were by far the richest in bacteria, yielding on an average of 7,550 per square centimetre.

As to the pathogenic bacteria that may occur on books, the following investigations are of great interest. Krausz inoculated seven guinea pigs with dirty pieces of paper from much-used books and they all died of peritonitis. The eighteen inoculated with pieces from clean books remained healthy. Du Cazal and Catrin found *Staphylococcus pyogenes* on an old book in a hospital. Most striking of all are Mitelescu's experiments. He took 60 much-used books that had been in a public library from six months to two years; he cut out the dirtiest parts, soaked them in salt solution, centrifuged the liquid and inoculated guinea pigs with the sediment. Nineteen died of septicemia, and twelve of streptococcus infection. He repeated the experiment with thirty-seven books from three to six years old. Fourteen of the guinea pigs died of septicemia, and fifteen contracted tuberculosis. The damp dirt on the older books was a good medium for tubercle bacilli.

The following abstracts are taken from the report made to the Board of Trustees of the Chicago Public Library upon books in that

library by Dr. W. A. Kuflewski and are of value as showing the germs to be found on books long in use.

These books were selected by Mr. F. H. Hild, Librarian, and Dr. Reynolds, the object being to get the books that were most worn and most soiled, and the examination was made by Dr. Adolph Gehrman, who reported as follows:

- D 2017a From delivery station, 14 years.  
19 Cultures from page 57, brown spot—negative.  
Cultures from torn places on cover.  
(A) Staphylococci and saprophytes.  
(B) Negative.
- C 7357 Delivery station, 20 years.  
Cultures from title page—negative.  
Cultures from title page—negative.  
Cultures from page 19—negative.  
Cultures from page 19—negative.
- H 2455c Delivery station, 6 years.  
Cultures from top of page 278—negative.  
Cultures from leather back—*Staphylococcus pyogenes albus*.  
Cultures from bottom edge of pages—*Staphylococcus pyogenes albus*.  
Cultures from top edge of pages—saprophytes and *S. pyogenes*.
- F 8346c Circulating department, 2 years: Popular juvenile.  
Cultures from leather back—negative.  
Cultures from top of pages—negative.  
Cultures from page 190—negative.
- F 494aa Circulating department, 26 years: Popular fiction.  
Cultures from spot on page 25—negative.  
Culture from leather back—negative.  
Cultures from bottom pages—negative.
- RR 281 Buck's Cyclopædia, 14 years: Reference book.  
Cultures from leather back—1 colony of *Staphylococci*.  
Cultures from edge of cover—1 colony of *Staphylococci*.  
Cultures from dirty page—*Staphylococci*.  
Cultures from clean pages—*Staphylococci*.

#### SUMMARY OF RESULTS.

Negative results: 3 books—C 735; 58 346c; and E 494aa.

Cultures from covers showing *Staphylococci*: 3 books—D 2017a, H 2455c, and

281.

19

1

Cultures from pages showing *Staphylococci*: 2 books—H 2455c and RR 281.

1

A series of cultures from the hands of two persons in the laboratory were made in the same manner and these showed a few colonies of saprophytes and *Staphylococci pyogenes albus*. In a general way these cultures were similar to those giving positive results made from the books.

The method employed in making these cultures was to take a few drops of sterile bouillon and with a platinum wire rub it upon the place from which the inoculations were made and then transfer this loop of bouillon to the blood serum boxes used by the department for diagnosis of diphtheria. These were placed in an incubating oven for forty-eight hours. The resulting colonies were examined microscopically.

Control cultures were made on several boxes by first placing the drop of bouillon on the sterile slide and then transferring it to the blood serum media.

In none of the cultures were diphtheria bacilli found. The *Staphylococcus pyogenes albus* is one of the pus bacteria usually found upon the skin of most individuals. The saprophytes are accidental non-pathogenic bacteria from the air, and are of no consequence.

Dr. Kuflewski states that "after personal investigation and examination of three sets of books taken at random from the shelves of the Chicago Public Library I am prepared to state that I found bacteria in large numbers in all the samples and that each book was more or less infected. These bacteria were in large numbers and were both pathogenic and non-pathogenic—the word pathogenic meaning 'disease-producing.'"

In many instances these bacteria do not harm, not even the pathogenic, because of the resistance of the tissue—being unimpaired—or because of the comparatively small numbers of bacteria which gain access to the tissues; but under favorable circumstances, such as a simple exposure to cold and especially to bronchitis, which is so prevalent in Chicago, a little wound or an abrasion of the surface of the body, a little scratch of the mucous membrane or of the skin, which as we all know is often treated as insignificant and is neglected, may be the means of introduction into the system of the most infectious disease germs. It is well known that a fresh wound absorbs bacteria and their toxins very rapidly.

I have had in my own experience a case in which I satisfactorily proved that a child contracted an infectious disease in the eye, from



the page of a book. Prof. Dr. W. A. Evans, who is an authority, states the case of a person who was infected with typhoid germs from books, which case was established beyond question. I had another case two or three years ago; a gentleman who was suffering from cancer in the roof of the mouth, in which the tongue and lips were also affected, was reading books from public libraries in this city for nearly two years and until I was called to treat him. He had been treated before by the "faith cures" and by the followers of Dowie. This patient was found expectorating minute pieces of his tongue and lips, which were a cancerous tissue, all over the pages of the book he read. That they were cancerous was not only proven by my own examination, but by that of Dr. LeCount, an eminent bacteriologist, who reported to me that the piece of tissue submitted was cancerous, containing cancerous cells.

Of course I prohibited this person from reading any more books from the libraries, and told his wife to be very careful as the disease was contagious.

In my own experiments I had no difficulty in obtaining colonies from the pages and bindings of all of the books examined, and I also obtained cultures of various forms from dust many years old, which according to the text-books, should have been destroyed.

*Flies.*—These insects are now known to carry germs. In some cases as many as six million have been found on a single specimen. In very few cases are libraries protected by screens; the fly just from a patient suffering from a contagious disease, or off the waste matter in a near-by cesspool, has easy access to the interior of the library, where, alighting upon a binding or page of an open book it proceeds to eject a number of germs with its excreta, or by rubbing its body with its forelegs, shakes large numbers off, which find ready lodgment, especially if the spot where the rubbing takes place is greasy, as is generally the case where a book has been much used or circulated for quite a number of times.

People do not seem able to overcome the vulgar habit of moistening the fingers in turning over the leaves of the books and again placing the finger on the lips each time to remoisten, never considering that each time he is, perhaps, transferring germs to fertile soil for propagation, resulting in sickness later on, or in case of a patient already suffering from disease, especially tuberculosis, helping to inflict another victim with the disease. And we all know that sick

persons, especially in the convalescent stage, spend a great deal of their time in reading books and magazines.

*Disinfection.*—This process in killing germs in books, although recommended, especially by those who have the disinfectants and the apparatus for sale, may be dismissed as of very little use, on account of the impossibility of the gases penetrating into the interior of the volumes, and in no case, even if the entire surface is reached, will they remove all of the spores.

*Sterilization.*—Both steam and hot air sterilization are of little value for books, because the first will cause the paper of the books to absorb the moisture, swell and deform the book, and while in the case of hot air sterilization, the heat would, by drying up all the moisture in the books, have the same effect, besides, in the case of books bound with leather, cause the leather to stretch and often break.

The heat also will absorb the moisture and the paper will become dry and brittle, lessening the life of the volume. At present I do not believe, that there is any method which may be depended upon to entirely eliminate the possibility of diseases being contracted through contact with fomites, such as books and the hundreds of other articles in daily use, constantly being transferred to a sick-room, returned and ready for another victim. I believe that some of the State Boards of Health are now beginning to recognize the futility of quarantining and disinfecting. Instead they are spending all their energies in improving sanitary conditions as to the necessity of cleanliness and the proper care of health. If a person using books or any other of the numerous articles named as conveying germs will use precautions as to the degree of cleanliness of the article they handle, and will take the proper care of their health, they need have no fear of contracting any disease by means of a book or any other article.

Suppose that a library did disinfect their books, what claim can they make that the book has no germs, after it has been placed on a shelf next to another book or been handled by a reader or one of the assistants. Dr. A. W. Doty, of New York City, states along the line of using disinfectants at intervals, "I know of nothing in public sanitation which is more farcical than the general or periodical disinfection of books with gaseous disinfectants for the purpose of preventing infection. These agents have no penetration of any account, and I have little faith in them for this purpose. I believe

that the careful dusting of the books and an abundance of fresh air and proper ventilation in a library is all that need be done under ordinary conditions."

He here touches the remedy, cleanliness, in relation to the books, but the same care that should be given to keeping the books clean should also be insisted upon for the employees and readers of libraries and all places where dust may accumulate.

A visit to almost any library will generally show, by placing the hands in back of the books upon the shelves, that there is a great deal of dust lying there. Very few libraries, even those recently erected, have had the vacuum system, which seems to be almost perfected, installed. Instead of making the reader wash his or her hands before using a book, it is very difficult for one to obtain access to the lavatory to wash his hands even if he so desires. In fact, there are some libraries which have no lavatories at all for the public.

Books are often placed on shelves in stacks, poorly ventilated and lighted. The results obtained in the library at Hawaii, whose books were constantly being destroyed by insects while stored in a dark, badly ventilated building, but was almost eliminated when transferred to a well-lighted and ventilated building, prove the value of pure air and sunlight. Not disinfectant plants, but sunlight, fresh air, the elimination of dust, and the proper cleanliness on the part of the employees and readers, is the way, not only to prevent books from becoming fomites, but also the people becoming carriers in this age of prevention.

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## EHRlich's CHEMOTHERAPY.<sup>1</sup>

HOW HIS LOGICAL, SYSTEMATIC CAMPAIGN AGAINST CERTAIN  
DISEASES HAS DEMONSTRATED THE VALUE OF SCIENTIFIC  
METHODS IN THERAPEUTICAL PROBLEMS.

BY HENRY P. TALBOT.

Chemotherapy has been called "a new science." It should, rather, be regarded as the designation of a scientific field in which therapeutics and chemistry intermingle in the solution of problems involving the principles of both of the older sciences, much as do physics and chemistry in so-called "physical chemistry," which is not, on that account, regarded as a "new" science.

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<sup>1</sup> Reprinted from *Science Conspectus*, March, 1913.

Therapeutics is defined as that branch of medical science " which deals with the composition, application, and modes of operation of the remedies for disease." But it has now taken on a somewhat broader, though less exact, meaning, and is understood to include the general administration of medicine, questions of hygiene and dietetics, and much that has to do mainly with the general well-being of the individual. That chemistry must be, as it has been for centuries, inseparable from the study of therapeutics is obvious, and the advance from the simplicity of the theory of Geber, according to which the animal organism was made up of only " sulphur " and " mercury " to our still very imperfect knowledge of the complex changes of physiological processes is, indeed, remarkable. But modern medical and chemical science is not content with the mere alleviation of the ravages of existing disease, that is, with the modifying or assisting of functions temporarily disturbed, but has struck more directly at the root of the trouble by devising means actually to destroy the causative agents and thus arrest the disease, or to render the animal organism inhospitable to these causative agents, as, for example, through the anti-toxins and the methods of preventive medicine in general.

All this had been done even before the advent of chemotherapy. What, then, is new about this combination of scientific effort in two allied fields? Essentially this: It is a logical, systematic campaign against diseases which are caused by the infection of the animal organism by parasites (*i.e.*, bacteria or protozoa) by means of chemicals which have not been found by empirical and more or less haphazard methods, but have been synthesized and built up solely for the purpose in hand, and as the result of researches which have called for the highest type of accurate observation and analytical reasoning for their execution. In this way it has been found possible to devise means by which the animal organism can be sterilized with respect to the parasites in question, and the consequent symptoms of disease can be arrested.

The development of this field is due almost entirely to Professor Paul Ehrlich, of Frankfort, and his co-workers. Dr. Ehrlich was educated as a physician, but has now become also one of the most accomplished and able investigators in the field of synthetic organic chemistry. A conception of the significance of his work can, perhaps, be best obtained by noting important phases in its progressive development.

More than thirty years ago Ehrlich began using coal-tar colors in his physiological studies, employing them as stains for preparations to be examined under the microscope. It is, of course, now commonly known that certain dye-stuffs appear to have a selective affinity for certain tissues of the body, or for certain parasites when residing within it, and these stains are in every day use by the pathologist. But it was not so thirty years ago, and Ehrlich first found that a dye-stuff known as methylene-blue, and its congeners, were the only colors which would stain live nerve tissue, and drew from this the important inference, which is at the basis of chemotherapy, that this was because of a particular receptivity for these dye-stuffs on the part of these tissues or parasites. It is easy to understand something of the importance of this use of these stains, or dyes, if it is recalled that the changes produced in the individual cells or tissues by drugs are not detectable even under the microscope in most cases, and that it is only through these stains that a knowledge of what has actually happened can be even approximately learned.

Ehrlich concluded from his observations that it was probable that, since these tissues and parasites possessed this receptivity for these specific bodies, there must be some definite effect produced as a result of the combination, if combination it were, and proceeded to conduct investigations in this direction. After some time these researches were rewarded, and in 1890 Ehrlich and Lappmann published a paper on the pain-relieving properties of methylene-blue, and, later, Ehrlich and Guttman found that the same dye was fatal to one type of the plasmodium, the parasite which causes malaria. As the latter field of investigation, that of the effect upon parasites, appeared very promising, they turned their attention to a particular class of parasites known as trypanosomes, because these could be more easily studied by the inoculation of mice.

The disease-producing parasites are sometimes of vegetable origin, as the bacteria, and sometimes of animal nature, as the protozoa. The trypanosomes are worm-like bodies, somewhat larger than bacteria, belonging to the animal class, and the diseases which they produce prevail most generally in tropical countries. Of these diseases, surra, most generally known in India among cattle, dogs and camels; nagana (tsetse-fly disease), known in Africa among animals in general; and mal de cadaras, known in South America among horses, are typical, while man is also attacked by the sleeping

sickness in the tropics. The scourge of syphilis is produced by a parasite known as the spirochete, which is closely allied to the others named, although it is still undetermined whether its nature is animal or vegetable. As will be seen, this particular disease has been found to be one of the most amenable to treatment.

As a result of his researches, Ehrlich formulated a theory regarding the behavior of the cells of living tissue, or of parasites toward foreign bodies. He conceives them as made up of a central "dominant body," which throws out "sidechains," to which he later gave the name receptors. These are of variable character, some being nutrient receptors, and others chemo-receptors, that is, receptors or certain definite chemical elements or groups of elements, known in chemistry as radicals. In a crude sense, the receptors may be likened to locks, and the nutrient or chemical bodies as keys, each fitting a particular lock, as, for example, the dyestuff methylene-blue already mentioned. The combinations thus affected may be beneficial to the cell, as in the case of the nutrients, or they may result in the poisoning and death of the cell, as in the case of the methylene-blue when brought into contact with the type of plasmodium referred to above, or quinine for plasmodia in general, a specific remedy for malaria discovered by empirical research.

Ehrlich and his co-workers, with extraordinary skill and industry, prepared several hundred dye-stuffs, studying the varying effects of alterations in chemical structure, each new compound having been logically selected as the result of laboratory tests of its parasitocidal efficiency. Of all these, very few finally withstood severe tests, possibly not more than ten in all, but the fact was established that it was possible in certain cases to sterilize the animal organism with respect to parasites, by this means, without, at the same time, poisoning the animal itself. They were also able to establish certain principles as to the chemical structure of the dye-stuffs most likely to be effective. They encountered, however, many difficulties. A dye which would attack and destroy a given parasite in a particular animal would not always do so in another species. Symptoms of disease would sometimes recur after varying intervals, and the parasites would then often exhibit peculiar resistance to further attack.

While these researches were still in progress, Uhlenmuth and Salmon published an account of instances of marked success in the destruction of the spirochete of syphilis, and the arrest of the disease, by the use of an arsenical compound known as atoxyl. Secondary

and seriously harmful effects to the patients were, however, the consequence of this treatment, but the parasiticial properties of this compound were so marked that Ehrlich turned his attention to it, in an attempt to so modify its effects upon the animal organism which was harboring the parasites, that its curative power might be made available.

The task was by no means a simple one. He first established the composition of the atoxyl as a para-amido-phenyl arsenic acid. The vast amount of work already done with the dye-stuff indicated certain lines of probable success, which, nevertheless, was only attained on the synthesis of the six hundred and sixth organic compound by Ehrlich and Kata, sometimes known as "606," and now designated salvarsan. Chemically it is dioxy-diamido-arseno-benzol, in which arsenic is associated with structural groups akin to those found in the dye-stuffs. A later preparation "914," known as neo-salvarsan, is said to be a combination of a salvarsan with sodium formaldehyde sulfoxalate, which is designed to overcome a certain difficulty in administration of the salvarsan, due to acidity of its solutions.

Ehrlich assumes that the parasite of syphilis, the spirochete, possesses among others, arsenio-receptors, and that through the combination with this arsenic compound the parasite is poisoned and dies. Ehrlich claims that in more than twelve thousand cases in which this drug has been administered by him, no single case of poisoning has resulted. The administration of the drug, which is intravenous, or intramuscular, requires, however, considerable skill and care. The treatment with salvarsan is often combined with that of mercury. There seems to be no doubt that this preparation exerts a specific and destructive action upon the spirochete, and has already resulted in the alleviation of an enormous amount of suffering (often hereditary and undeserved) from this dreadful scourge. It is still too early to make final statements as to the permanence of the cures affected although there is much reason for hopefulness. It should, however, be noted that this chemotherapeutic treatment, unlike the anti-toxin treatment for certain other diseases, does not at all produce immunity from later infection from the same disease. Indeed, there is some evidence to show that cases of re-infection are distinctly harder to treat successfully than those of initial infection. The cure of advanced cases of the disease naturally, presents greater difficulties, because of secondary disturbances of the vital organs, but many of these have been materially alleviated.

The progress made in the chemotherapeutic treatment of diseases produced by other trypanosomes, notably that of the "sleeping sickness," has been less marked up to the present. Something has been gained, but no specific drug comparable with salvarsan in its efficiency has yet been found.

It is, however, recorded that in Surinam a hospital was established to treat cases of another tropical disease known as the yaws. In the course of eight days three hundred and twenty-eight cases were admitted, and at the end of fourteen days the last patient was discharged, cured, and the hospital had to be closed.

In another field the work of Ehrlich has led to procedures which are of the greatest promise in the study of the processes involved in the progress of medical and physiological research, namely, so-called "vital staining." By means of the injection of dye-stuffs into living organisms, it is possible, because of the selective receptivity of certain tissues or parasites, for a particular color, to trace the movement of bacilli, and to watch the changes which they occasion in the living organism itself. The same procedure is employed in the study of healthy tissue.

To Ehrlich's clear, analytical mind, exceptional executive ability, fine technique, and extraordinary industry is due not only the procedure by which certain particular diseases may be arrested, but a splendid example of logical attack upon other similar problems; which offers great promise for the future, even though, as in the case of the anti-toxins, one marked success may not be at once followed by others of equal moment. He has demonstrated, in a way which cannot be detailed in the scope of this article, that the test-tube experiments made in the laboratory with a particular drug upon a special parasite cannot be alone relied upon as an index of the effect upon it of the same drug when it is harbored by the living organism, since the action is essentially modified by that organism, and he has advanced theories which at least help in the understanding of the possible reasons for the variations in behavior thus observed. Even though Ehrlich's chemotherapy may not be, in an exact sense, a "new science," it must be acknowledged to be a most fruitful and helpful combination of the principles of two well-recognized and time-honored sciences for the benefit of mankind.



## OIL OF SANDALWOOD.<sup>1</sup>

By E. M. HOLMES.

The gradual, but steady, increase in the price of sandalwood oil during the last few years has naturally given rise to enquiries concerning its cause. Neither the growing use of the oil for medicinal purposes, nor the large demand for the wood in India and China, can sufficiently account for it. There is, however, a possible cause that has apparently not received the attention it deserves from merchants in this country. During the last 30 years or more, *Lantana* and *Casuarina* plants have been introduced into sandalwood plantations with the idea of their shade helping the growth of the young sandal plants, and it appears that concurrently with a diseased state of the *Lantana*, the sandal plants have become affected with what is known as the spike disease.

A most interesting account of this disease is given by Mr. F. S. Mason in the *Pharmaceutical Journal* in 1903 (May 30th, p. 756), which gives an excellent idea of the character of the disease, and of the extent to which the plantations are affected. One remark in this paper is well worthy of notice, viz., that "within five years it has swept whole tracts of country, and unless some means can be devised to check its ravages, it is only a question of time for the plant to become very rare, if not extinct." So convinced was the Mysore Government of the importance of finding a means to check the disease, that in 1907 the Maharajah of Mysore offered a prize of 10,000 rupees to anyone who could discover the cause of the disease, and devise a curative treatment for it. But although the offer remained open until 1910 no one succeeded in winning the prize.

The cause of the disease was investigated on behalf of the Indian Government by Mr. Barber and Dr. Butler, and they came to the conclusion that it was not due to any animal or vegetable parasite, but was connected with the disc-like suckers at the extremities of the roots of the sandalwood tree, by which it attaches itself to the roots of other plants and obtains nourishment from them (*Indian Forester*, xxxiii, 1907, p. 199). That no curative means of arresting the disease has yet been devised is evident from

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<sup>1</sup> The *Perfumery and Essential Oil Record*, June, 1913, 161.

a statement published last October in the same journal, to the effect that the disease still continues with dire results, and that in two districts alone some 70,000 sandal trees had to be uprooted.

In order to obtain an idea of the probable cause of this disease it is necessary to pay some attention to the life history of the plant, so far as this is known. As already mentioned, the sandal tree is a root parasite, obtaining its food by means of suckers, which it attaches to the roots of other trees. It has been ascertained by Rama Rao that there are at least 144 species of plants which the sandal tree attacks in this way, as proved by experiment with sandalwood seedlings, and he gives a list of 252 plants which are found growing near or with the sandal tree, but are as yet not known to be utilized as a source of food by this tree. It does not appear to be equally nourished by all of its host plants, and the condition of the tree depends upon the vigorous and healthy state of its host. Thus it is known that a plant on which it will thrive in one district fails to keep it in a healthy state in another, where the conditions are unsuitable to the healthy growth of the host plant. This requirement of the sandalwood tree is well shown by an observation recorded in the *Indian Forester*, (xxxI, p. 191), that when a trunk of *Heptapleurum* was cut down, the sandal plant attached to its roots began to wither, but when new shoots formed on it the sandal plant began to revive. The sandalwood tree sends out roots for 150 feet or more, and therefore requires a comparatively loose and well-drained soil which the roots can easily penetrate and spread in. In a natural state it flourishes at an altitude of 1500 to 4000 ft., the best yield of oil being obtained from trees growing between 2000 to 3500 ft., on loose volcanic soil mixed with rocks, and preferably ferruginous in character. It requires to be shaded by thickets above which it can form a head of leafy branches.

Although in rich soil it grows more luxuriantly, less scented wood is formed, although, as the tree furnishes more wood, the proportion is about the same. It is considered that the richness of the wood in oil depends more upon elevation and exposure, since, although the tree grows luxuriantly at 700 ft., the wood is said to be totally devoid of scent at that altitude (*Indian Forester*, xxvi, pp. 1-50, 1900).

The experiments made by Rama Rao indicate that the physical conditions of soil and drainage affect the development of the root-branching system. The soil needs to be well drained, as the seed

rots in soil where stagnant water is present, more readily than in most plants.

The seed of the sandalwood tree germinates freely in the thickets where the tree grows, within a month of being sown, although germination may occur any time during three months or longer, but if the seed germinates in open ground where it does not meet with other roots, the seedlings soon wither and die. The young plants for plantations must therefore be raised by planting them with other plants on whose roots the seedlings can feed as soon as they have exhausted the nourishment of their own seed lobes, which lasts for about two months. The seeds are therefore planted in short wide tile tubes resembling drain pipes, but shorter, so that the young seedlings can be planted out without disturbing their root attachments. This planting out is done when they are about 4 ins. high or rather more than a year old. If allowed to grow larger there is likely to be injury done to the roots in planting them out. After planting out, the seedlings require to be gently but copiously watered until well established.

Experiment has shown that the best plants to grow with the seedlings are *Pongamia glabra*, *Gossypium arboreum*, *Albizia Lebek* and *Cleistanthus collinus*.

The seedlings need protection from animals, as the foliage of the sandalwood plants proves very attractive to them. Cattle and goats will greedily eat the foliage whenever they see it, and deer will leap over the obstructing bushes to get at it, and hares will creep through the thicket to reach it.

As the seedlings in a wild state reach only a height of 3 ins. the first year, and 12 ins. the second year, they are easily destroyed. It is only in the fifth or sixth year they appear above the surrounding bushes and form a leafy head. At this time the stem is about 1 in. in diameter.

It takes 18 to 25 years before the tree is fit to yield oil. With respect to the spike disease, the trees attacked by it present the appearance of being dead, but on careful examination many leaves are seen to be scattered over the tree at the end of the stiff branches, but they are very small, and form small terminal tufts, hence the name "Spike" disease. The shoots are found to be full of starch, indicating that the plant has not been able to utilize its stored-up nourishment. The disease is pronounced to be infectious, because

all sandal plants, in plantations where it occurs, have died, whilst solitary trees are still thriving.

From the above facts, recorded by various observers, it becomes evident that the sandalwood tree requires plenty of room so as to be able to select vigorous hosts to feed it; that it requires soil porous enough to enable its roots to spread readily, and that, therefore, if too closely planted, it may easily be starved, especially in hard or heavy soil. The fact that isolated trees thrive in a natural condition also indicates that the disease is one of mal-nutrition, whilst the presence of starch in the withered shoots indicates the absence of a suitable enzyme to transform it into soluble food.

Apparently no attempts have as yet been made to ascertain the chemical constituents that the tree contains, and therefore needs, although Peterson (*Pharmaceutical Journal* (3), xvi, page 575) found that Macassar sandalwood was rich in iron (7.5 pc) and contained traces of manganese. The latter metal is believed to be connected with the activity of enzymes, and it is possible that a deficiency of it in the soil may injuriously affect the growth. Research is also evidently necessary to ascertain if the tree selects one ingredient for its nourishment from one tree and other ingredients from other species, as it is well known that certain enzymes can split up other bodies than those on which they usually act.

There is evidently much to be done before the cause of the disease and the means to prevent it can be ascertained.

Regarding the subject from the commercial side, the possibility of other sources of sandalwood suggests itself. The world's supply of sandalwood oil is at the present time chiefly derived from the trees grown in Southern India, only a comparatively small quantity coming from the Islands of Timor and Sumba via Macassar. The yield from Mysore last year was 2469 tons of sandalwood, exclusive of chips and sawdust. The average price, including chips and sawdust, was 471 rupees as against 461 rupees per ton during the previous decennial period.

The only other oil that at present competes with the East Indian sandalwood oil is that of *Amyris balsamifera* L., a tree belonging to the natural order Burseraceæ, the wood of which is imported from Venezuela, and is known in Europe as West Indian sandalwood. It competes, however, only in medicinal use, not in perfumery.

Of the 20 or more known species of *Santalum*, which are dis-

tributed over Asia, Australia, New Caledonia and Polynesia, several were rendered almost extinct by the ruthless destruction of the trees during the first half of the last century, and are not now available in quantity for commercial purposes. These include *S. Freycinetianum*, Gaud., of the Sandwich Islands, *S. Hornei*, Seem., of Eromanga, *S. insulare*, Bert., of the Marquesas and Dociety Islands, and *S. Yasi*, Seem., of the Tongo Islands, and *S. Austro-Caledonicum*, Vieill., of New Caledonia. The wood of these trees was chiefly collected for the Chinese market, and not for the distillation of oil. None of these trees, so far as is known, yields an oil equal in fragrance to that of *S. album*.

A log of wood of *Santalum Yasi* from the Indian and Colonial Exhibition was distilled by Mr. C. Unney in 1886, and a sample of the oil sent to Messrs. Schimmel and Co., who considered it inferior both in perfume and therapeutical effect to that of *Santalum album*. The yield appeared to be  $6\frac{1}{2}$  per cent., although the real percentage might have been less, as an unusual amount of water separated from the oil in the winter weather.

Of the trees yielding sandalwood in Australia, some of which were formerly classed in the genus *Santalum*, the oils are known only in a few cases. That of *Fusanus spicatus* R. Br. (formerly *Santalum cygnorum*) or West Australian sandalwood oil, is distilled to some extent in West Australia, but is considered by Gildemeister and Hoffmann to have an unpleasant resinous odor, and not fit to be used as a substitute for East Indian sandalwood oil. It is, however, the nearest to the true sandalwood oil, and contains 75 per cent. of alcohols, which have, however, not been positively identified with santalol, but owing to the small yield of oil (2 per cent.) and the expense of labor in Australia, although the tree is fairly plentiful, it cannot compete with the Indian oil. That of *F. acuminatus* R. Br. (formerly *Santalum Preissianum* Miq.) known as South Australian sandalwood, yields a vivid cherry-red oil, from which crystals separate out on cooling. It has a different, somewhat rose-like odor, and a different composition and specific gravity to that of East Indian sandalwood. *Exocarpus latifolius* R. Br., a West Australian plant, may perhaps yield some of the West Australian sandalwood oil, but there is no evidence that it yields an oil resembling that of true sandalwood.

Several fragrant woods are known under the name of sandalwood in other countries; the wood of *Osyris tenuifolia*, Engl., a

native of Kilmandscharo, in East Africa, has been imported into Germany under the name of East African sandalwood. The oil was described in 1908 as being bright brown in color with an odor intermediate between that of vetivert and gurjun balsam, but quite different from sandalwood (Pflanzenwelt Ost. Afrika C. 167, Schimmel's Report, November, 1908, p. 109).

The Madagascar "Sandalwood," of which the native name is apparently "Hasoranto," is exported from Tamatave in the North of Madagascar to Zanzibar, and thence to Bombay, where it is known as taggar wood, and is largely used as a cheap substitute for sandalwood for funeral pyres. The wood is of a dark brown color, and yields a dark-colored thick oil, with an odor slightly resembling sandalwood, but which for medicinal or perfumery purposes could by no means be used as a substitute for it. Its botanical source is unknown, but is supposed to be a Lauraceous tree.

New Zealand Sandalwood.—The wood of *Olcaria Traversii*, F. Muell, was exhibited at the International Exhibition in 1886 under the name of bastard sandalwood. It belongs to the Family of Compositæ, but nothing appears to be known of its oil.

Cochin China Sandalwood.—This is ascribed by Baillon to *Epicharis Lourcirii*, Pierre, Fam. Melacæe, but I have not seen a specimen.

Guiana Sandalwood.—The oil has already been described (*P. & E. O. R.*, 1911, p. 79). Dr. Giessler, of Leipzig, is of opinion that the oil is probably derived from three species of the genus *Acroclidium*, or *Ocotea* (Schimmel's Report, October, 1911, p. 82). It does not resemble sandalwood oil in odor and is not known to do so therapeutically.

Ibean Sandalwood.—The wood of *Brachylana Hutchinsii*, Hutchinson (Family Compositæ), is known under this name. The tree grows near Nhairobi and in forests near the coast at an elevation of 5000 to 6000 feet. The timber is white, hard, easily worked, and scented when freshly cut, and is not subject to the attacks of white ants. The native name of the tree is "Muhugu." It does not appear to have been exported as yet, the tree being only described three years ago in the Kew Bulletin, 1910, p. 126. The plant is illustrated in the *Icones Plantarum*, 292a.

It is obvious, therefore, that at present there is no oil known that can altogether take the place of sandalwood oil, and until a

means of combating the spike disease has been discovered and the best method of cultivation of the tree has been ascertained, the price of sandalwood is likely to rise, especially since it takes from 18 to 25 years for the tree to arrive at maturity and to grow scented wood.

The chemical constitution of the oil does not hold out much hope that it will be an easy matter to produce it synthetically, for even if santalol can be produced from piperidine, there are evidently other constituents that go to form the odor of the oil, and unless these can be ascertained it is not likely to take the same place in perfumery or medicine as the oil distilled from *Santalum album*.

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## ABSTRACTS OF SOME PAPERS READ AT THE 1913 MEETING OF THE PENNSYLVANIA STATE PHARMACEUTICAL ASSOCIATION.

BY JOHN K. THUM, PH.G., Philadelphia, Pa.

### WHAT IS THE QUALITY OF PANCREATIN ON THE MARKET?

BY CHARLES H. LA WALL.

An examination of some pancreatin by the author disclosed the interesting fact that it was adulterated with powdered malt. Of course this raised the starch converting power, and, as the author states, as this test is the only one applied sometimes and as the general appearance of such a sophisticated sample is normal, a more than superficial examination of pancreatin is necessary to insure good quality.

### STERILIZATION IN PHARMACY.

BY A. PARKER HITCHENS, M.D.

The author in a very interesting and illuminative manner describes the possible purposes of sterilization in pharmacy and gives in detail the various methods which have been found to be of value.

### CROTALIN—COLLECTION, PRESERVATION, CHEMISTRY AND ACTION.

BY WALTER ROTHWELL.

Attenuated snake venom, obtained from *Crotalus Horridus*, commonly known as "rattlesnake," has obtained some vogue in recent years in the treatment of epilepsy. The author briefly de-

scribes the method of obtaining the venom, its preservation, chemistry, and action. It is given hypodermatically and its action is to increase the time of the coagulation of the blood.

### THE DETECTION OF CANE SUGAR IN HONEY.

BY CHARLES LA WALL, PH.M.

The author concludes that it is impossible to detect added cane sugar in honey by means of a qualitative test; being present normally in small amounts its quantitative determination is preferably accomplished by means of the polariscope. Invert sugar is the kind usually added and can be easily detected in honey that has never been heated.

### OREGON AND CANADA BALSAM OF FIR.

BY J. G. ROBERTS AND M. M. BECKER.

The writers state that because of the scarcity of Canada Balsam of Fir for the last year or two a suitable substitute is desirable. And as a substitute Oregon Balsam of Fir is offered to the trade. As is well known this product closely resembles Canada Balsam of Fir.

Finding that the literature on Oregon Balsam contained little information the authors obtained some balsam from a known source and endeavored to obtain data as to tests for identity and purity.

It differed in the main from Canada Balsam in viscosity, solubility in alcohol, and in response to the magnesium oxide test. The Oregon Balsam is thinner; it is completely soluble in alcohol in contradistinction to the official balsam which yields a turbid solution. Canada Balsam when mixed with 20 per cent. of its weight of magnesium oxide previously moistened with water, becomes solid. The Oregon does not solidify even when mixed with 60 per cent. of its weight of magnesium oxide. It was also noticed that the Oregon Balsam does not dry as readily as the Canada Balsam, a quality which renders it inferior to the latter for microscopical work.

### SOCOTRINE ALOES.

BY C. J. DENNEY.

The author remarks that although the United States Pharmacopœia definition of aloes is broad enough to allow recognition of all varieties of genuine aloes yet it neglects to describe some samples



as imported. It is often received in barrels in a pasty condition, containing nearly twice the amount of water permitted by the U. S. P. It is further remarked by the author that when in this condition the only recourse is rejection of the shipment as abnormal as to its physical appearance, or, it being satisfactory as to identity and purity, to dry so that sample is of proper U. S. P. quality. A tabulation of five samples is given; all contained twice the quantity of water allowable; they also failed to pass the alcohol test for limit of gums, dextrans and impurities. While Kraemer and others state that aloes should not yield more than 4 per cent. of ash all of these samples were slightly higher. As is well known and has been for some time, no aloes is obtained from Socotra.

### THE MICROSCOPIC EXAMINATION OF OINTMENTS.

BY FRITZ HEIDLBERG AND CHAS. E. VANDERKLEED.

The value of an ointment, the authors state, consists mainly in the fineness or subdivision of the active ingredient suspended in the vehicle. And to properly determine when the ointment has been manipulated long enough for the active ingredient to be uniformly and evenly divided they advise the use of the microscope. They state that this is the only satisfactory way to tell whether uniform results have been obtained. They also give their technic for preparing slides for this purpose and illustrate by showing micro-photographs of mercury ointments.

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### BOOK REVIEWS.

DIGEST OF COMMENTS ON THE PHARMACOPŒIA OF THE UNITED STATES OF AMERICA (8TH DECENNIAL REVISION) AND ON THE NATIONAL FORMULARY (3RD EDITION) FOR THE CALENDAR YEAR ENDING DECEMBER 31, 1911. By Murray Galt Motter and Martin I. Wilbert.

The foregoing title, known also as Bulletin No. 87, Hygienic Laboratory, needs little introduction to the progressive members of the pharmaceutical profession. It speaks for itself. It is sufficient to say that the literature covered in this review embraces matters that must, if thoroughly and painstakingly studied by the

two revision committees, result in the publication of a Pharmacopœia and National Formulary that will be regarded as authoritative and the last word in pharmaceutical matters.

References to the great mass of literature consulted is complete in every respect and comments relating to the legal status and development of pure food and drug laws, scope, analytical data, clinical tests, biologic products and vegetable drugs are abstracted with the main points of the papers brought out. This is as it should be, as it enables a worker to see at once if a reference is worth while consulting.

It is particularly gratifying to note that references of a practical nature in regard to pharmaceutical preparations and suggestions as to their improvement, both as to formula and method of preparation, are much in evidence.

• The "digest" also places at the disposal of the revision committees references to all literature pertaining to international standards. Every decade brings us closer to a realization of the fact that the question of unification of pharmacopœial preparations is becoming a matter of supreme importance. Rapid means of travel and communication are largely responsible for this.

Foreign Pharmacopœias always bring forth considerable comment and criticism from workers and experts from various parts of the globe and last year was no exception. The collaborators of the "Digest" make this fact plain in their references to literature that comments on the German, Russian, Italian, French, Swedish, Swiss, Austrian, Japanese, Dutch, and British Pharmacopœias and the British Pharmaceutical Codex.

Part III of this Bulletin is devoted to a most comprehensive review of the literature relating to comments on official articles 504 pages being required to show what has been said and done in this field of endeavor, and also illustrating what a tremendous amount of reading the preparation of this valuable government publication required for its completion.

JOHN K. THUM.

THE PROPAGANDA FOR REFORM IN PROPRIETARY MEDICINES.  
Reprinted from the Journal of the American Medical Association.  
Eighth Edition, 1913.

There are many people who take as gospel truth anything they see in print. There are a great many other people who, while they

know better than to do this, are unable to discriminate and so are almost as easily led as the others. Then there are many people afflicted with some ailment, or think that they are, who clutch, like a drowning man after a straw, any statement which seems to bear upon their case.

To satisfy the "needs" of people like these there is a host of firms who manufacture remedies for every conceivable trouble, and to eliminate the need of having a physician they include in their packages circulars which purport to give complete directions of use. So extraordinary are some of these statements that anyone even only very superficially acquainted with the facts would prick up his ears at hearing them. But not so with the gullible public. The more extreme the statement, the more absolute dependence they place on the product.

Truly, this proprietary medicine venture is no more than a psychological game between the manufacturer and the public, only the public is not aware that it is playing the game. Here are some of the psychological weapons the manufacturer has at his command:

1. As one bows down to a man who is well dressed and imposing in appearance, so one worships an ordinary drug or food (or even a worthless one) when it is clothed in a dignified name.

2. As the average illogical mind believes that what comes after must be due to what goes before, the deduction is easily made that if a person recovers after having made use of some remedy, the remedy deserves the credit. This is termed the *post hoc, ergo propter hoc* argument. The folly of course lies in the fact that in the great percentage of cases the patient would have recovered without any remedy.

Yes, the Propaganda for Reform in Proprietary Medicines, which is a bound volume of reprints, might well be called "A Study in the Psychology of Advertising Worthless Products." A former book of reprints entitled "Nostrums and Quackery" is relative especially to those nostrums which are exploited only—or chiefly—to the public. The volume under consideration, however, relates to those products which are exploited to the physician and includes also some of those in the other volume where there seemed to be an "overlapping."

Some 120 proprietaries are considered, the schemes by which they are foisted upon the public through the medical profession are discussed with numerous reproductions of illustrations of advertise-

ments, and chemical formulas and therapeutic properties are given.

A striking feature is the prominence which must be taken by the products of large well-known manufacturing houses who are making a mighty good thing out of the credulity of the public with no regard to the ethics of the profession.

A. K. LOBECK.

ARBEITEN AUS DEM PHARMAZEUTISCHEN INSTITUT DER UNIVERSITÄT BERLIN, by H. Thoms, v. 10, including the work of the year 1912, Urban & Schwarzenberg, Berlin, Wien, 1913, 220 pages, with two illustrations.

This volume like the ones preceding it reflects the work done in the Pharmaceutical Institute of the University of Berlin, by Prof. Thoms and his associates, and includes a total of 35 contributions, under five general headings: 1, Contributions from the division for the examination of drugs, specialties and secret remedies; 2, reports on organic chemical work; 3, microchemical work; 4, reports from the division for the examination of foods and technical products of the Colonies; 5, general discussion. The whole is followed by an index of four double column pages. The first section of the book includes a systematic review of the new remedies introduced during the year 1912, and reports the analytical examination of a number of proprietary preparations. The phytochemical work reported in this volume includes observations on the production of menthol in Germany and in the German Colonies, and an examination of the seed of *Strychnos kongofera* for strychnine. Lenz discusses the production and use of microchemical reagents in a paper covering eight pages, and Thoms, in a very comprehensive paper, reviews the problems of pharmaceutical education in Germany and other European countries.

Altogether the volume is well up to the high standard that has been established by those preceding it and the renewed energy with which the work on so-called new remedies is being prosecuted bodes well for the general progress of pharmacy along satisfactory lines.

M. I. W.

ARBEITEN AUS DEM PHARMAZEUTISCHEN INSTITUT DER UNIVERSITÄT BERLIN, herausgegeben von, Prof. Dr. H. Thoms.

This publication, the tenth annual volume, consisting of 220 pages, presents a record of the work accomplished during 1912 at

the Pharmaceutical Institute of the University of Berlin under the direction of Dr. H. Thoms, the Director.

It also gives evidence that the German pharmacist, acting through this pharmaceutical institute, is alive to the need of protecting the medical profession and the public against fraud, secret medicines and mendacious advertising. Here, in our own country, the pharmacists have been so busy worrying about price protection on nostrums and telephone rates that the medical profession took the bull by the horns, so to speak, and through its national organization, the American Medical Association, organized a permanent committee, and named it the Council on Pharmacy and Chemistry. What this council has done since its organization is known to all progressive pharmacists. And its efforts for better things are surely showing results. One has but to glance over the proceedings and reports of some of the medical and pharmaceutical societies to realize that we are at the dawn of a new era as to things pertaining to these two professions.

The investigations of the laboratory workers of this German institution covered a wide field in the domain of synthetic chemistry, particularly as regards the output of the dye houses of that country, specialties of all kinds, and secret remedies and nostrums of all kinds.

Under the classification of Analgesics, Antipyretics, and Antirheumatics, considerable attention is given to such chemicals as Melubrin, one of the more recent antipyretics, said to be useful in rheumatism and resembling in its effects the salicylates, chemically it is sodium-phenyl-dimethyl-pyrazolon-amido-methan-sulphonate; Atophan, said to be useful as an antirheumatic in so far as it aids in the elimination of uric acid and chemically known as phenyl-quinolin-carboxylic acid; Novatophan a modification of atophan and tasteless while the latter is bitter; Aspirin Soluble which is the calcium salt of acetyl-salicylic acid; Luminal, a sedative and hypnotic, the chemical name of which is phenylethylmalonylurea; Brophenin, a combination of bromine with phenetidin and chemically known as bromisovaleryl-amino-acetate-p-phenetidin; many others too numerous to mention are also considered.

Besides giving considerable space in this publication to the investigation of products (*Kolonialprodukte*) from the German colonies, both as to their chemistry and pharmacognosy, there also appears an exposure of some of the nostrum emmenagogues found

on the German market. One of these consisted of small quantities of oil of cinnamon and cloves in 12 per cent. of alcohol. For two ounces of this wonderful and efficient (?) preparation the modest sum of one dollar was asked. Another, called "Menstruationpulver" consisted of a very poor quality of powdered Roman Chamomile, and for the small (?) sum of seventy-five cents the buyer received a package containing 35 grammes.

An interesting report is given of an examination of a fixed oil sent to the Institute by a German missionary pastor from Venezuela. This oil is used by the Indians in the region of Orinoco as a remedy in the treatment of tuberculosis. The results are reported as good. This oil is yellow in color, slightly cloudy, and in odor and taste somewhat resembling olive oil; at room temperature fluid; on cooling there was separated a small mass of fatty acid which, on warming, disappeared. At 12° C. the oil congealed to a soft butter-like mass. It was miscible in all proportions with ether, chloroform, petroleum benzine, benzol, and carbon disulphide and on the contrary immiscible with absolute alcohol and glacial acetic acid. On the addition of HCl and furfural no red coloration appeared. The test for cotton-seed oil by the addition of sulphur and carbon disulphide gave negative results. The constants were ascertained in the usual manner and found as follows:

Specific gravity at 15° C. ....	0.9125
Acid number .....	4.46
Saponification value .....	200.45
Iodine value according to Hübl after 2 hours.....	69.9
Iodine value according to Hübl after 6 hours.....	71.0
Unsaponifiable constituents .....	0.48 per cent.
Refractometer number in a Zeiss butter-refractometer at 25°.	59-60
Optical rotation in 200 ccm.-tube.....	0

The oil also gave the reaction for elaidin. Hehner's method for the separation of the fatty acids was used and the melting point of these was found to be 30.31°, the congealing point 22° and the saponification value 195.5. The fatty acids also gave an iodine value of 75.25. After recrystallization from alcohol twice, the elaidic acid showed a melting-point of 51°. Experiments on mice proved this Ceje-Öl, as it is termed, to be non-toxic. Whether it will be of any more value than other better-known fatty oils in the treatment of tuberculosis remains to be proven clinically.

As one reads through this volume, depicting the work done at this institute, the impression is gained that the aim of the workers is the scientific one, the desire for the *truth*; the truth about those remedies for which there may be a legitimate use and which are more or less ethically introduced, and the exposure of those remedies which are secret in composition and for which extravagant claims are made.

JOHN K. THUM.

“A HANDBOOK OF USEFUL DRUGS.” A selected list of important drugs suggested for the use of teachers of materia medica and therapeutics and to serve as a basis for the examinations by state medical examining and licensing boards. Prepared under the direction and supervision of the Council on Pharmacy and Chemistry of the American Medical Association. Press of the American Medical Association, 535 North Dearborn Street, Chicago, 1913.

It does not require the gifts of a seer or the abilities of a prophet to venture the opinion that this rather diminutive volume of 167 pages is destined in the near future to have a decidedly far-reaching influence on the teaching and on the practice of therapeutics and, consequently, is designed to have an equally important bearing on the future development of pharmacy and the efficiency of pharmacists generally.

Conscientious students of medical economics have long appreciated the waste of energy, money and even life resulting from the haphazard or ignorant misuse of drugs and medicines so general a decade or more since. Some nine years ago the Council on Pharmacy and Chemistry of the American Medical Association made its first onslaught on quacks and quackery in the medicine supply business and although the Council at that time had fair reason to believe that it might be assisted in its efforts by at least the more progressive of professional pharmacists, this expected coöperation has not been forthcoming, in this country at least. Medical practitioners, largely through the American Medical Association, have been compelled to stand practically alone in their fight against the purely commercial spirit in the practice of pharmacy of to-day. The little book before us is the latest step in this warfare, representing as it does the fundamentally constructive work of the Council on Pharmacy and Chemistry, as the earlier work “Propaganda for Reform” represents the destructive work of the same body, and the now well-known book, “New and Non-official Remedies” represents a compilation of reasonably good material that is offered for future in-

clusion in the recognized *materia medica* of conservative medical practitioners.

The object of this, the latest of the three books offered by the Council on Pharmacy and Chemistry of the American Medical Association, is perhaps best shown by quoting rather liberally from the preface, not necessarily exactly but rather the purport of the statements made, so as to avoid occasional repetition:

"Many of the articles in the *Pharmacopœia* and in the *National Formulary* are worthless or superfluous. The repeated efforts that have been made to eliminate at least the more useless of these articles have uniformly encountered the assertion that the articles objected to are used somewhere by some one, and that they should, therefore, be officially recognized and authoritatively defined.

"For a number of years men active in the work of the Council on Medical Education and in the Confederation of State Examining and Licensing Boards have been trying to restrict instruction and examination in *materia medica* to the more important drugs. These efforts apparently failed, so far as the Committee of Revision of the U. S. P. is concerned, but the suggestions have been taken up and elaborated by the Council on Pharmacy and Chemistry and the result is this volume on useful drugs.

"The book is offered as a fundamental list of drugs and preparations with which all medical students and practitioners might be expected to be familiar, and to which, therefore, state examining and licensing boards might largely or entirely confine their examinations in *materia medica*. As it now stands, it embodies a total of about 455 headings including 265 titles of drugs and chemicals, 137 pharmaceutical preparations, 13 cross references and 40 general definitions or descriptions of forms of medicines."

It is confidently predicted that an intelligent and critical use of these selected drugs will prove their general sufficiency, and show definitely that many drugs now discussed in text books and officialized in *pharmacopœias*, are, to say the least, superfluous. A careful study of this book is also well designed to demonstrate that many newly discovered or widely exploited proprietary preparations have no appreciable advantage over established drugs and preparations whose limitations and possible untoward results are generally well known.

Pharmacists and teachers of pharmacy should acquaint themselves with the nature as well as the intent of the volume. The last word on a limited list of useful drugs has not as yet been said, but



the agitation will undoubtedly do much toward insuring a more uniform and better supply of recognized, standard drugs, by placing responsibility for the identity and purity of drugs and preparations on the dispensing pharmacist, where it rightly belongs. By ultimately restricting the number of drugs and preparations used it will be possible to provide adequate supervision of the medicines dispensed; and thus the pharmacist will eventually come to occupy the place he rightly deserves as an important factor in safeguarding public health.

M. I. W.

WAR DEPARTMENT: Office of the Surgeon General, Bulletin No. 3. Studies of Syphilis. By Charles F. Craig, Captain, Medical Corps, U. S. Army, and Henry J. Nichols, Captain, Medical Corps, U. S. Army, with introduction by Major Frederick F. Russell, Medical Corps, U. S. Army.

This Bulletin, published for the information of medical officers by authority of the act of Congress approved August 23, 1912, and with the approval of the Secretary of War, is striking evidence of the fact that the wonderful advances made in the last decade for the diagnosis and treatment of syphilis are being made use of and appreciated by the medical men of the army. In no branch of medicine has more rapid progress been made. And, as pointed out in the introduction, "it is noteworthy that medicine is indebted to laboratory workers and research institutions, and not to the practical syphilographers, for this phenomenal progress."

Exclusive of the introduction the Bulletin consists of a series of seven papers commencing with a study of the *Spirochæta pallida*, its morphology and cultivation. Under the head of immunity the interesting statement is brought out that there is no true immunity following an infection from this parasite. A person once infected and cured can be reinfected. Opinions contrary to this were long held by the medical profession.

The diagnosis of syphilis by the complement fixation test, or Wassermann test, as it is more generally known, is gone into very fully. That this test has proven of great value in the army for diagnosis and control over treatment is attested by the experience gained from the performance of 12,000 reactions.

Ehrlich's great discovery, salvarsan and neosalvarsan, naturally, have been used and the behavior of these arsenic combinations with the benzol ring, in the treatment of syphilis is very fully gone into. The superiority of these drugs over mercury as a specific is clearly

proven; yet, in the light of our present knowledge, the consensus of opinion is that a wise combination of mercury plus salvarsan or neosalvarsan intravenously procures the best results.

The work recorded in this Bulletin clearly emphasizes the fact that the Medical Corps of the Army, in its care of our fighting men, possesses unusual facilities for the scientific observation, study, and treatment of this disease.

JOHN K. THUM.

ESSENTIALS OF PRESCRIPTION WRITING. By Cary Eggleston, M.D., Instructor in Pharmacology, Cornell University Medical College, New York City. W. B. Saunders Company, Philadelphia and London.

Within the confines of this small volume which consists of only 115 pages, a medical student or graduate physician may find all the information necessary to equip himself in the principles of prescription writing, a branch of medicine in which most graduates in medicine find themselves utterly at sea when first starting practice. Some overcome this handicap and some do not; to the latter we most heartily recommend this handy little book, although, as a matter of fact, it may be read with profit by all who practise medicine.

This book consists of ten chapters which embody the fundamentals in a sequential manner; the chapter devoted to Latin grammar is brief but thorough—the author has evidently learned the art of saying much in few words—while the suggestions offered as to flavoring, coloring, and vehicles (aqueous, hydro-alcoholic and alcoholic), if carefully studied and faithfully carried out by physicians, would soon result in diminishing, if not abolishing, the proprietary medicine evil.

JOHN K. THUM.

GENEALOGY OF THE DESCENDANTS OF THOMAS FRENCH, with Some Account of Colonial Manners and Doings, together with One Hundred and Fifty Picture Prints Compiled and Published by Howard Barclay French, of the Seventh Generation. Vol. II, Philadelphia. Privately printed, 1913.

Oliver Wendell Holmes once wrote that "Philadelphia was the center of genealogy." With this new contribution which is now completed, Dr. Holmes' views are confirmed. A very extended review of the first volume was given in this JOURNAL in June, 1909, p. 309. The work is handsomely gotten out and will stand as a monument to Mr. French.

# THE AMERICAN JOURNAL OF PHARMACY

*FEBRUARY, 1914*

## THE OIL OF ARGEMONE MEXICANA.

BY KSHITIBHUSHAN BHADURI, M.Sc.

### HISTORICAL.

This is an American plant, which has run wild all over India. It may easily be known by its glaucous, prickly, thistle-like leaves, bright yellow flowers, and milky juice. The latter is used as an application to ulcers and in combination with the juice of *Aristolochia bracteata* is given internally in syphilis and gonorrhœa. In the Concan the juice with milk is given in leprosy. The seeds and oil have been used by European physicians. The oil in doses from 30 to 60 drops is a valuable remedy in dysentery and other affections of the internal canal. Fluckiger found 4 to 5 gms. to have a mild purgative effect. An extract made from the whole plant has been found to have an aperient action and the milky juice to promote the healing of indolent ulcers.

The oil used for examination was obtained by pressing the crushed seeds in a screw press in the laboratory in presence of the author. The chances of adulteration were thus avoided.

### EXPERIMENTAL.

Some of the crushed seeds were submitted to steam distillation; the distillate had a slight opalescence and a very pungent odor, but no oil came over.

47.1176 gms. of the crushed seeds were exhausted in a Soxhlet apparatus with petroleum ether, the latter evaporated off when 10.4966 gms. of a thin brown colored oil was left behind. Hence the percentage of oil is 22.3. According to Charbonnier the seeds contain 36 per cent. of oil.

The petroleum ether extract has a pale greenish-yellow color with a green fluorescence, if it be evaporated at the ordinary temperature, the oil left behind has an olive green color. If this be

either left exposed to the atmosphere or heated on the water bath it gradually acquires a rich brown color. If it be still further heated the color deepens and it diffuses a very intense odor, like that of the juice of the fresh plant.

The pressed oil was of a deep brown color, had a mild odor and was tasteless. The freshly obtained oil was very thin, but on keeping it gradually thickened. Crossley and Le Sueur (*Journ. Soc. Chem. Ind.*, 1898, 991) say the fresh oil is of orange color and has a slight but distinctive smell.

The mixed fatty acids had a paler color and were very thin.

The oil on keeping exposed to the atmosphere or on treatment with an oxidizing agent deposited a very small quantity of a red crystalline substance (M.P.  $172^{\circ}$  C.).

The oil gradually thickened with the lowering of temperature, until at  $17^{\circ}$  C. the clear liquid became turbid, the temperature remained constant for a little time at  $16^{\circ}$  C. Charbonnier's oil remained clear at  $-8^{\circ}$  C. and Fluckiger's oil at  $-6^{\circ}$  C.

The specific gravity was determined at two different temperatures, at  $28^{\circ}$  C. and at the boiling point of water. In the former case it was 0.9117 and at the latter it was 0.9007. Charbonnier obtained a specific gravity of 0.920, Fluckiger 0.919 at  $16.5^{\circ}$  C. and Crossley and Le Sueur 0.9247–0.9259 at  $15.5^{\circ}$  C.

The refractive index obtained with a Pulfrich's refractometer was  $43^{\circ} 34'$  at  $32^{\circ}$  C. or 1.46552. With a butyro refractometer Crossley and Le Sueur obtained at  $40^{\circ}$  C. a refractive index of 62.5.

The oil and absolute alcohol were miscible in any extent. For the determination of its solubility in dilute alcohol the following method was adopted. In a stoppered graduated tall cylinder a measured volume of oil was introduced, to this a known volume of alcohol was added and then water added drop by drop with continuous shaking till a permanent turbidity was obtained. The total volume was read off and from this when the volume of oil and alcohol was subtracted the volume of water added was obtained.

TABLE OF SOLUBILITY IN ALCOHOL OF DIFFERENT STRENGTH AT  $32^{\circ}$  C.

Oil.	Water.	Alcohol.
10	9	12
10	15	20
10	22	32
10	28	42
11	24	42
15	24	45

116.4 c.c. of  $\frac{N}{10}$  alcoholic potash (calculated) were required for the saponification of 3.4828 gms. of oil; hence the saponification value is 185.5. The saponification obtained by Crossley and Le Sueur is 187.8-190.3.

The oil was acetylated by boiling with acetic anhydride and purified, then dried with anhydrous Sodium Sulphate. 3.23 gms. of oil thus obtained required 122 c.c. (calculated) of  $\frac{N}{10}$  potash for complete saponification. The saponification value of the acetylated oil was 213.4 and deducting from this 185.5, the saponification value, we got 27.9 as the acetyl value.

The oil contained a large proportion of free fatty acid for which determination 3.5998 gms. of oil was dissolved in 50 c.c. of neutralized alcohol and a little phenolphthalein solution added and titrated with  $\frac{N}{10}$  alkali. It was found that 94.3 c.c. was necessary for neutralization, hence the acid value is 146. Two specimens of oil were examined by Crossley and Le Sueur who found 6.0 and 83.9 as the acid value.

In the aqueous solution left after the decomposition of the soap with an acid, the presence of the following fatty acids was proved (1) acetic acid proved by the Cacodyl test and (2) valeric acid by the formation of the ester.

In a weighed flask 2.3696 gms. of oil was taken and dissolved in 50 c.c. of chloroform, and Bromine gradually added till no further absorption took place. It was then evaporated off on the water bath and dried. The weight of the brominated oil now was 4.7912 or the increase in weight was 102.2 per cent. This is the bromine value.

The iodine value of the oil is 106.7. That obtained by Crossley and Le Sueur is 119.91-122.5.

2.7 gms. of oil was saponified, then decomposed with dilute sulphuric acid and submitted to steam distillation. 0.33 c.c. of  $\frac{N}{10}$  alkali was required for neutralization of 100 c.c. distillate. Therefore the Reichert-Meisel value is 0.61.

From 1.8426 gms. of oil the author obtained 1.7295 gms. of a mixture of insoluble fatty acids and unsaponifiable matters. The Hahnemann's value is 94.02. The above authors obtained 95.07.

The glycerol was estimated by the Benedikt and Zsismondy process. This consists in oxidizing the glycerol to oxalic acid by

potassium permanganate. From the amount of oxalic acid obtained the weight of glycerol was calculated. It was found to be 15.48 per cent.

6.1996 gms. of oil was saponified, alcohol evaporated off; it was then dissolved in water and extracted with ether. The ethereal extract on evaporation left behind .1418 gm. of residue or the oil contains 2.29 per cent. of unsaponifiable matter.

The elaidin produced by the oil was an orange-colored, dough-like mass. The reaction was very violent.

When sulphur chloride was added to a solution of equal volume of oil and carbon disulphide a violent reaction ensued, the whole mass frothing up; a very sticky mass was left behind.

When 10 gms. of sulphuric acid was added to 50 gms. of oil the rise of temperature was 65° C. The Maumene test was 65° C.

• The rise in temperature on brominating 1 c.c. of oil was 16.5° C.

The oil gave no characteristic color reaction with sulphuric acid even when it was diluted with carbon disulphide. The color was blackish-brown in the former case and in the latter case light brown.

On shaking the oil with nitric acid it acquired a deep brown color and the acid a deep red color. On heating it a violent reaction ensued, a pale orange-colored scum was formed when the whole was allowed to stand over night.

For the determination of oxygen absorption power a quantity of lead was prepared by Livache's method; about a gram of it was spread upon a watch glass and a weighed volume of the oil was spread on it by allowing it to drop on different places. This was weighed. The weights on each successive day were noted till there was no further increase in weight.

GAIN IN WEIGHT OF 1.3437 GMS. OF OIL.

Days.	Increase in weight.	Per cent. increase.
1st day.	0.269	2.002
2nd day.	0.107	0.8
3rd day.	0.0084	0.6
5th day.	0.0152	1.1
6th day.	0.0059	0.44
8th day.	0.0065	0.48
9th day.	0.0015	0.1
10th day.	No increase.	

Total gain in weight till constant = 5.522.

39 c.c. of the oil was fractionally distilled at 15 mm. pressure when the following fractions were obtained.

Temperature.	Weight of fraction.	Remarks.
215°-217° C.	3.81	Instantly solidified.
217°-224° C.	9.08	Solidified but contained some liquid.
224°-228° C.	9.24	Liquid, on prolonged keeping a few crystals separated out.
228°-231° C.	6.45	Pale brown liquid.
231°-235° C.	2.79	Greenish liquid.

#### EXAMINATION OF THE MIXED FATTY ACIDS.

The specific gravity at 28° C. is 0.9065 and at the boiling point of water 0.8889.

2.0688 gms. required for saponification 90.4 c.c. of  $\frac{N}{10}$  alkali.

The saponification value is 194.

0.40745 gms. of oil absorbed 0.6003 gms. of iodine from a solution of iodine and mercury bichloride in absolute alcohol. The iodine value hence is 147.4.

To find out the neutralization value, 3.6638 gms. of the mixture were diluted with 50 c.c. of neutralized alcohol, a drop of phenolphthalein solution added and titrated with a normal solution of caustic potash. It was found 12.64 c.c. were necessary for this purpose. Hence it follows that 193.2 mgms. of KOH were necessary for the neutralization of one gram of the mixture. The mean molecular weight is found by dividing 56.1 by that found necessary for the neutralization of one gm. of oil.

Let  $M$  be the molecular weight and  $n$  the weight of KOH in gms.

$$\therefore M = \frac{56.1}{n}$$

now  $n = a \times 0.0561$  ( $a$  number of c.c.'s of normal KOH).

$$\therefore M = \frac{56.1}{a \times 0.0561} = \frac{1000}{a} = \frac{1000}{3.45} = 289.8.$$

3.3303 gms. of oil gave 2.5847 gms. of liquid fatty acid by the lead-salt-ether process. Therefore, 77 per cent. of the total fatty acid was liquid fatty acid.

It was found that the oil did not contain any stearic acid.

The lactone value of the mixed fatty acid was the difference between the saponification and neutralization values, .8.

The titer test of temperature of turbidity of the mixed fatty acid is 22° C.

The mixed fatty acid contains 8.14 per cent. of lauric acid as was found by fractional distillation of the oil *in vacuo*.

Chemical Laboratory, PRESENCY COLLEGE, Calcutta.

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## AN ASSAY PROCESS FOR QUININE IN TABLETS.

BY SIDNEY F. FIESELMANN, Peoria, Ill.

A rapid method for the quantitative estimation of quinine in tablets, containing no other chloroform soluble constituents, that are not expelled at a temperature of 125° C., which has been successfully used by the author with accurate results, is the following:

Count out a sufficient number of tablets, so as to make the total number represent 10 grains of quinine or quinine salts, based on the quantity claimed on the label. If the quantity stated per tablet cannot be made to come out in a whole number of tablets, take the number of tablets, which contain about 10 grains and make the required correction. Weigh the tablets counted out accurately on an analytical balance. Multiply this weight by two and call it *X* grams. Then powder a sufficient amount of tablets and force all through a number sixty sieve. In case of coated tablets be careful not to loose any particle of the hard coating or parts of tablets during the process of powdering and sifting. Then mix thoroughly after this operation, so as to insure a uniform representative mixture. Weigh up *X* grams of this powder in a 100 c.c. Erlenmeyer flask, add 50 c.c. of chloroform, accurately measured, stopper and shake well. Now add 5 c.c. of ammonia water U. S. P., stopper well and shake thoroughly for 20 minutes. Let stand for about 12 hours in a cool place, with occasional shaking, and decant the chloroform into a separatory funnel, stopper well and allow to stand until separation takes place. Take a 5 cm. plain folded filter paper, on a small 60° glass funnel, moisten with a little chloroform, taking care not to have any chloroform drop into the measuring cylinder or any remaining in the tube of the funnel. Then withdraw enough of the chloroformic solution in the separating funnel and filter the same through the moistened filter paper into a 50 c.c. measuring cylinder until 25 c.c. are obtained.



If this 25 c.c. of filtrate is colorless or of a light straw color, transfer it to a tared beaker of 60-100 c.c. capacity, rinsing the cylinder with three portions of 10 c.c. of chloroform and adding the same to the chloroform solution in the tared beaker. Then evaporate the chloroform carefully on a water bath. If the filtrate is highly colored, from the coating, coloring matter, or resinous substances in the tablets, transfer the same into a clean separatory funnel, rinse out the cylinder as before, adding the same to the chloroform solution in the separatory funnel, and shake out with three portions of normal sulphuric acid, 15, 5, 5 c.c. respectively, each portion diluted with 5 c.c. of distilled water. Collect the combined acid aqueous solution in a clean separatory funnel, add a small piece of red litmus paper, make distinctly alkaline with ammonia water U. S. P. and shake out with three successive portions of 25, 15, and 15 c.c. of chloroform, collecting the same in a tared beaker. After the chloroform has evaporated, redissolve the residue in 5 or 10 c.c. of ether and let evaporate spontaneously.

Finally, place the tared beaker, containing the quinine residue in a drying oven and heat to a constant weight at 125° C., cooling the tared beaker each time in a desiccator before weighing. It usually requires from one to three hours of heating until the weight is constant. The tared beaker should be chemically clean and heated for at least one half hour at 125° C. and cooled in a calcium chloride desiccator, before it is weighed and the chloroformic solution added.

If exactly 10 grains of quinine or the salts of quinine were taken as per label the residue should weigh the following:

For Quinine Alkaloid U. S. P. (Quinine + 3H <sub>2</sub> O) .....	0.5553 Grams.
For Quinine Bisulphate U. S. P. ....	0.3830 Grams.
For Quinine Hydrobromide U. S. P. ....	0.4963 Grams.
For Quinine Hydrochloride U. S. P. ....	0.5296 Grams.
For Quinine Salicylate U. S. P. ....	0.4457 Grams.
For Quinine Sulphate U. S. P. ....	0.4814 Grams.

Tablets containing substances like calcined magnesia as a drying agent, do not filter rapidly by the above method. The water in the ammonia water forms a gelatinous mass with the magnesia, which prevents rapid filtration and sometimes stops it altogether. In that case the following method is suggested. Measure out in a 50 c.c. measuring cylinder, 5 c.c. of spirit of ammonia U. S. P., add a sufficient quantity of chloroform to make exactly 50 c.c. Use

this as a menstruum and follow the other directions as given above omitting the ammonia water. This last method cannot always be used on account of the alcohol in the spirit of ammonia U. S. P., which dissolves more substances than the chloroform would alone and so the residue would not be pure quinine. On the other hand chloroform alone will not dissolve anything but the quinine of the substances usually found in quinine tablets.

In order to obtain sufficient chloroformic filtrate from tablets containing an unusual large quantity of other material and only a small amount of quinine, it may be necessary to increase the chloroformic menstruum from 50 c.c. to 100 c.c. or more, filtering off one half the quantity used, following the instructions given above.

SUTLIFF AND CASE CO., Peoria, Ill.

## U. S. P. 1900 MENSTRUUA.

BY H. C. HAMILTON.

It seems almost superfluous to call attention, at this late date, to certain points in the 8th Revision of the U. S. P. which need correction in the forthcoming 9th Revision. Particularly does it seem unnecessary in view of the fact that the objectionable features to which this article alludes have been pointed out before and by several critics. The excuse for doing so, however, if any is necessary, is that the data here published may be of value to those who have under consideration for the 9th Revision of the Pharmacopœia the menstrua for the extraction of the digitalis series of heart tonics. The menstrua to which we refer are for the preparation of: I. F. E. Digitalis; II. F. E. Squill; III. F. E. Convallaria.

I. The first two of these were referred to by Houghton and Hamilton<sup>1</sup> in the following words:

"3. Fluidextract digitalis, U. S. P. 8th Rev., 48 per cent. alcohol.

"Average potency of eleven samples at time of manufacture 55 H. T. U. per c.c. Three and a half years later 35 H. T. U. Average loss about 10 per cent. yearly.

"A very important point should be noted in this connection; namely, the menstruum adopted in the last U. S. P. for the preparation of fluidextract digitalis is much less desirable than the U. S. P. 7th Revision in at least two respects. Repeated trials show that it is

almost impossible to get a finished product containing the full number of H. T. U. of the standard we had previously adopted, the average being as above stated, 55 H. T. U. per c.c., while with drug of the same quality when the 7th Revision menstruum is employed no difficulty is experienced. Owing to this it was decided to no longer attempt to assay physiologically the 8th Revision product and to take such statement referring to it off the label, but, in order to supply the medical profession with a full strength fluidextract of the drug, it was decided to prepare such with a menstruum containing a larger per cent. of alcohol which could be assayed and so labelled. In the second place the loss in potency of the 8th Revision is about 10 per cent. per year, while with the 7th Revision it is less than one-half as great, or about 4 per cent. The results coincide quite closely with those following the change made in the menstruum for the fluidextract of squill except that the loss in activity was greater in the latter drug, as pointed out by Houghton<sup>2</sup> three years ago. In this paper several methods of physiological assay showed very clearly that a serious mistake had been made in changing to acetic acid as a menstruum. The writers feel certain that any one who has tried the 8th Revision menstruum for fluidextract digitalis has found that it is much less satisfactory from a pharmaceutical point of view, to say nothing of the loss in potency."

To this we wish to add data since obtained on F. E. Digitalis as follows:

Menstruum.	Per cent. Activity.
50 per cent. alcohol.....	100
80 per cent. alcohol .....	120

The above samples were prepared from one lot of drug, using 100 grams and extracting until exhausted.

Another small sample of drug carefully extracted by both methods and tested gave results as follows:

with 50 per cent. alcohol.....	110 per cent. of standard.
with 80 per cent. alcohol.....	140 per cent. of standard.

A sample of drug extracted with several strengths of alcohol gave the following results:

Menstruum.	Per cent. Activity.
94 per cent. alcohol.....	90
75 per cent. alcohol.....	140
62.7 per cent. alcohol.....	125
50 per cent. alcohol.....	110

The following table shows the tests of commercial lots of F. E. Digitalis, U. S. P. 8th Rev. (*a*) before and (*b*) after an attempt to improve the quality by concentrating the extract.

Number.	Tested.	Per cent. Activity.
1 ( <i>a</i> )	8/4/9	85
1 ( <i>b</i> )	8/19/9	90
2 ( <i>a</i> )	7/20/9	85
2 ( <i>b</i> )	8/4/9	85
3 ( <i>a</i> )	3/4/9	60
3 ( <i>b</i> )	4/2/9	100
4 ( <i>a</i> )	1/31/8	80
4 ( <i>b</i> )	2/8/8	80
5 ( <i>a</i> )	5/23/7	75
5 ( <i>b</i> )	6/1/7	83

• Further data on 20 samples of the preparation show results of first tests ranging from 50 to 100 per cent. standard and averaging exactly 78 per cent.

The standard referred to is the average activity obtained from 12 lots of crude drug, botanically of first class quality, selected at random and extracted with 62.7 per cent. alcohol, the official menstruum of the U. S. P. 7th Revision. The activity was determined by the frog method described by Houghton<sup>3</sup> as a means of standardizing the heart tonics of the digitalis series. In that article attention was called to the enormous variation in samples of the crude drug for sale on the open market.

The value of such a method is also shown when endeavoring to extract from active material all the therapeutically active substances and to establish by experiments on other than the human subject the relative activity of extracts obtained by means of various menstrua.

The above results speak for themselves, but if additional authority is needed it should be sufficient to note that the menstrua for making tinctures and fluidextracts of digitalis in the official Pharmacopœiæ of the world, specify, almost without exception, a percentage of alcohol in excess of that official in the U. S. P. 8th Revision. The menstruum adopted in 1906 by the Brussels Conference is 70 per cent. alcohol and it is to be hoped that the Revision Committee will be influenced by this in adopting an official menstruum for the 9th Rev. of the U. S. P.

II. As noted before in the abstract from the AMERICAN JOURNAL

OF PHARMACY<sup>1</sup> a mistake was certainly made in adopting for the preparation of F. E. Squill, U. S. P., 8th Rev., a menstruum composed of a 10 per cent. solution of Acetic Acid. This is so far from being ideal for extracting the active substances from Squill bulb that it is practically impossible to prepare an extract representing the activity of the crude drug.

Comparison of the activity of F. E. Squill, U. S. P., 1890 and 1900, was made by Houghton<sup>4</sup> as follows:

"Comparative Strength of Fluid Extract of Squill Prepared from the Same Lot of Drug According to the United States Pharmacopœia of 1890 and 1900:

- "1 U.S.P., 1890, 140 per cent. as active as standard fluid extract.
- "2 U.S.P., 1890, 140 per cent. as active as standard fluid extract.
- "3 U.S.P., 1900, 60 per cent. as active as standard fluid extract.
- "4 U.S.P., 1900, 60 per cent. as active as standard fluid extract.

"It may be observed that activity of both products is high as compared with the results given in Table 2. This probably is due to the great care exercised completely to exhaust the drug and to the high quality of the drug.

"In order to meet any objections that might be offered against the results as shown by the special method of assay employed, the work was checked by experiments on dogs showing the comparative activity of the two products in producing changes in the blood-pressure, which is perhaps the most characteristic physiologic action of the members of the digitalis series."

The results of the latter experiments are here recorded in tabular form for more convenient reference.

#### EXPERIMENT I.

	F. E. Squill, U. S. P., 1890.		F. E. Squill, U. S. P., 1900.	
	Before injection.	After injection.	Before.	After.
Pulse Rate .....	100	96	116	138
Blood-pressure .....	46	54	48	45

In this experiment 0.3 c.c. F. E. Squill, U. S. P., 1890, was injected at 10.45 A.M. into the femoral vein of an anæsthetized dog. Then at 2.41 P.M., when the effect of the first injection had passed, the same amount of F. E. Squill, U. S. P., 1900, was injected.

In the second experiment the order of injection was reversed another dog being used for the test, and the same amount of each preparation injected.

## EXPERIMENT II.

	F. E. Squill, U. S. P., 1900.		F. E. Squill, U. S. P., 1890.	
	Before.	After.	Before.	After.
Pulse Rate .....	102	144	100	94
Blood-pressure .....	47	46	52	50

NOTE.—In both cases the U. S. P., 1900, preparation increased the rate and lowered the pressure. This is directly opposite in effect from the characteristic action of the heart tonics in general and from that of the F. E. Squill, U. S. P., 1890, from the same drug.

In this case again a stronger alcohol is better. If the drug is finely ground and extracted with menstrua containing 60 per cent. or less of alcohol, it swells so that percolation is either entirely or almost prevented. It becomes necessary either to cut the bulb without grinding or to mix with sawdust in order to have it sufficiently open to percolate properly. An additional objection is in the large amount of gummy, water-soluble extractive obtained with such menstrua. A fluid extract of better appearance, better keeping quality and containing practically all the available activity of the drug, can be obtained by the use of 80 per cent. alcohol. Repeated experiments have shown the excellence of this menstruum over that of the 7th or 8th Revisions of the U. S. P.

III. Fluid Extract Convallaria, U. S. P., 1900, is not so open to criticism as the others but the menstruum is not entirely satisfactory. There are certain advantages to be gained by using a stronger alcoholic menstruum than that prescribed in the 8th Revision U. S. P. While these advantages are more apparent when experiments are conducted on a manufacturing scale than when small experimental lots of fluid extract are prepared, even in the latter case the advantages are very real.

Several experiments have been carried out, of which the following is used as an example:

A small lot of drug was divided into two portions, one of which was extracted as prescribed in the U. S. P.; namely, with 62.7 per cent. alcohol, the other with 80 per cent. alcohol. These extracts were carefully concentrated to fluid extract volume and tested for activity by the method previously cited, with the following results:

Menstruum.	Per cent. Activity.
62 per cent. alcohol	100
80 per cent. alcohol	120

The advantages to be gained from using a stronger alcoholic menstruum for extracting convallaria roots and rhizome are not merely the greater activity obtainable, but in the improved appearance of the extract and its greater stability. It contains less of the gummy extractives and more alcohol, both of which are desirable features, as they affect deterioration, while the 20 per cent. increase in activity from the use of 80 per cent. alcohol is no less desirable.

It is to be hoped that those in charge of revising the forthcoming U. S. Pharmacopœia will consider these suggestions.

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From the Research Laboratory of PARKE, DAVIS & Co.,  
Detroit, Michigan.

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### THE PHYSIOLOGICAL STANDARDIZATION OF THE HEART TONICS.\*

BY PROFESSOR WILLIAM A. PEARSON, of The Hahnemann Medical College  
of Philadelphia.

"The Physiological Testing of the Heart Tonics," which is the subject assigned for my discussion, is a very inaccurate title.

A satisfactory definition of a tonic has never been given, much less, a heart tonic. The word physiological is not appropriate because when any active drug is given the normal processes of the body are no longer physiological.

For these reasons, such a subject as "The Pharmacologic Standardization of Drugs Having a Particular Action on the Heart" would be far more fitting.

Since Digitalis is the most important member of the group of drugs known as "heart tonics," a discussion of the methods of standardizing this drug will be first considered.

#### MEDICINAL USE AND THERAPEUTIC ACTION OF DIGITALIS.

It is well known that Digitalis has had a place in domestic and medicinal therapy for centuries, and many of you know that a Bir-

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\* A special lecture given at The Philadelphia College of Pharmacy, December 8, 1913.

mingham physician by the name of Withering,<sup>1</sup> published in 1785 the first reliable observations of the medicinal properties of this drug. The diuretic properties of Digitalis were first observed, but after the middle of the last century its ability to slow the heart so impressed the medical profession that Digitalis was, and is even to this day, often used indiscriminately for all conditions where the heart beat is irregular or rapid. It can now be demonstrated that Digitalis is only of particular value in a very limited number of diseases of the heart and mainly in auricular fibrillation.

So far as showing the rate of the heart beats is concerned, it may be laid down as a law, that Digitalis is far less effective when the rhythm of the heart is normal than when there is auricular fibrillation.<sup>2</sup> Most authors state that digitalis causes constriction of the blood-vessels and consequently a rise in blood-pressure, yet I have not been able to demonstrate more than slight variations in blood-pressure in test animals, although various lots of tinctures, fluid extracts and proprietary preparations have been tried.

Mackenzie<sup>3</sup> has made numerous observations on various classes of patients and refutes the idea that the administration of Digitalis has a tendency to produce fatal syncope, provided the drug is stopped as soon as nausea and vomiting appear or when the heart rate falls below 50 per minute.

When the rhythm of the heart is normal the first symptom is loss of appetite, if drug is continued, vomiting, feeling of malaise, headache, and very little diarrhoea may be reported.

Famulener and Lyons<sup>5</sup> state that the digitalis glucosides act not only on the heart but directly on the central nervous system, first stimulating then depressing it. Cushny<sup>6</sup> states that "the chief therapeutic use is to counteract certain changes in the circulation, which result in the blood accumulating in the veins in too large quantities while the arteries are less filled than usual. In cases of dilation of the heart with a weak and insufficient systole, its action is almost specific.

"In these cases the action is very simple—the increased ventricular systole approaches the normal, the output of the heart is increased, and in some cases the dilation is diminished by the direct action of the drug. The effect is an increased velocity and pressure in the arteries and improved nutrition of the whole body."

There is no doubt that Digitalis relieves distress and dropsy and has been directly responsible for numerous cures, yet it is possible



that these favorable results may be attributed to some other reason than its effect on the heart, *per se*.

It is needless to say that Digitalis has been given thousands of times when its use was not indicated and doubtless its failure to produce favorable results under improper conditions has been responsible, more than once, for condemnation of the particular preparation of digitalis being used.<sup>4</sup> It has been repeatedly stated that analogous preparations of digitalis made by various manufacturers differ markedly in strength, that digitalis preparations rapidly deteriorate and that only the leaves of the first year's plant are active. It is no doubt true that analogous digitalis preparations differ markedly in strength,<sup>7</sup> but it is very doubtful if the usual galenical preparations deteriorate rapidly,<sup>8</sup> or that only the leaves of the first year's plant are active.<sup>9</sup>

It is possible, but not at all probable, that only the digitalis plants which are in flower are physiologically active and this need not exclude the first year's plants as John A. Bornemann<sup>10</sup> has shown me a digitalis plant with plenty of flowers on it, although it was a plant of the first year's growth. Certain it is that the therapeutic action of digitalis as stated by various authors is sadly confusing and no doubt much of this confusion is due not alone to clinical reports where digitalis was not indicated, but to the pharmacologic variability of the preparations themselves.

#### CHEMISTRY OF DIGITALIS.

Almost every pharmaceutical chemist of note has tried to isolate, unchanged, the complex active principles that are present in digitalis. The great Schmiedeberg and Kiliani agreed that the four glucosides which they separated and called digitoxin, digitalin, digitalein and digitophyllin, possess a true digitalis action. They separated, in addition, other glucosides such as digitonin, digitin and digitoflavin, but they considered these decomposition products. Several carbohydrates which came from the decomposition of the glucosides, were also described.

When one looks up the vast literature on the chemistry of digitalis it is quite evident that different glucosides are sometimes given the same name by different authors and *vice versa*.

Recently Kraft<sup>11</sup> has contributed an admirable article on this subject and his work is now generally accepted. He claims that both Schmiedeberg and Kiliani worked with German digatalin, a commercial product made largely from digitalis seeds, hence their results are

not reliable for digitalis leaves. Kraft has isolated a new active glucoside which he calls Gitalin, which probably has the chemical formula  $C_{28}H_{48}O_{10}$ . This glucoside is amorphous but forms a crystalline hydrate,  $C_{28}H_{48}O_{10} \cdot 4H_2O$ . Gitalin readily decomposes in any solvent except chloroform into anhydrogitalin  $C_{23}H_{46}O_9$ , which on hydrolysis, with a dilute acid in the presence of alcohol, changes to anhydrogitaligenin  $C_{22}H_{34}O_8$  and a sugar which was found to be identical with Kiliani's digitoxose. Another new glucoside was also isolated. This he called Gitin, and it is inactive physiologically. It is crystalline and melts at  $265^\circ C$ . It is considered similar to, but not identical with, Kiliani's digitonin.

Digitoxin is often considered the chief active glucoside in digitalis and chemical determinations of this constituent have been frequently made in the hope of finding a relationship between the digitoxin content and the therapeutic activity, but the results in almost every case have proved a failure.<sup>12</sup> If the digitoxin from a given amount of drug is isolated it will be found that the total amount of digitoxin is very much less toxic than the amount of drug from which it was obtained, hence it seems absolutely necessary to resort to pharmacological standardization if any definite idea of the therapeutic strength is desired.

#### PHARMACOLOGIC STANDARDIZATION OF DIGITALIS.

At least three distinctly different pharmacologic methods have been proposed for the standardization of Digitalis—the frog method, the guinea pig method, and the cat method.

#### THE FROG METHOD.

The frog method was first proposed by Houghton in 1898.<sup>13</sup> He found that "fairly accurate data could be obtained from the application of a solution containing Strophanthin, Digitalin, etc., to the laid-bare frog's heart, by comparing the action of the drug thus tested with that of a sample of known strength." After much experimental work this method was replaced by the use of a simpler one—namely, the determination of the minimum lethal dose for frogs under definite conditions. Although the original method as modified by Houghton gives quite satisfactory results, yet various workers have proposed certain changes in the conditions under which the test is to be made. For example, twelve hours was specified as being the length of time that observations should be made after injection of the

frogs. As this is usually inconvenient, these observations were made after one hour, two hours, six hours, or twenty-four hours. Some workers began to pith the frog at the end of one hour and make a direct examination of the condition of the heart, for it was found that sometimes frogs would be apparently normal yet their hearts had been stopped by the drug.

Dr. Hale<sup>14</sup> observed that more concordant results were obtained when the frogs were kept at the uniform temperature of 22° C. It would neither be interesting nor instructive to relate the various modifications that have been proposed for the Houghton method.

Edmunds and Hale,<sup>15</sup> Edmunds and Cushny,<sup>16</sup> and Focke<sup>17</sup> have specified various conditions under which the "frog test" is to be made, but none of these methods make any provision to *standardize the frogs that are used*.

It is known that variety, weight, sex, season, and temperature affect the resistance of frogs and hence it is possible to obtain different results with different lots of frogs. In order to eliminate these factors of unknown significance in any particular case, Houghton and Hamilton have suggested that a standard be used in testing the resistance of every lot of frogs, at the time the test is made. Upon these data "The Heart Tonic Unit"<sup>18</sup> is computed in every case.

The standard they propose to use is crystalline Strophanthin which is prepared from an authentic specimen of the official drug, *Strophanthus Kombé*, and has been studied in detail by Braun and Closson.<sup>19</sup> The outline of the present method as modified by Houghton is as follows:

Frogs should all be of same species, a convenient variety is the *Rana Pipiens*. They should all be of weights between 15 and 35 gm. and the weights should not vary more than 25 per cent. in any one assay. Before being used the frogs may be kept in any convenient place where the water can be frequently changed and kept at a temperature of about 22° C. During the test the frogs can advantageously be kept in wire cages with sheet iron bottoms, standing in trays of running water, but the depth of water in the cages should not exceed one-half an inch. Scales for weighing the frogs should be accurate within 0.5 gm. The necessary apparatus consists of volumetric flasks, cylinders, graduated pipettes and a 1 c.c. pipette graduated in hundredths of a cubic centimetre and fitted with a hypodermic needle or drawn out into a fine point for injecting.

The solution to be injected should not contain more than 10 per cent. alcohol and the dilution should be made with physiological salt solution (0.85 per cent. NaCl).

The doses are calculated on the weight of the frog, *i.e.*, the M. L. D. is the minimum lethal dose, per gram weight of frog. For example, when the frogs are of average resistance the M. L. D. of Strophanthin is 0.000,001 gm. per gram weight of frog, *i.e.*, for a 30 gram frog the lethal dose of Strophanthin is .000,03 gm., which should be so diluted that this amount is contained in approximately 0.5 c.c. Several series of tests are necessary to establish the activity of any sample of unknown strength and since the frogs vary in resistance among themselves and also because of conditions more or less beyond control, the standard Strophanthin must be tested at the same time. When the M. L. D. of sample and of standard are obtained the activity can readily be expressed in Heart Tonic Units (H. T. U.) by reference to a table.

In the method just given the observations are to be made at the end of twenty-four hours, hence the one-hour method has certain advantages when several series are desired on a single sample as soon as possible. When the one-hour method is used it is necessary to not consider all frogs that have not absorbed the dose injected.

#### THE ONE-HOUR METHOD.

"In this method the frogs are secured and kept in the manner already described, weighed, and such a dose is injected that the heart will be found in complete systolic contraction at the end of exactly sixty minutes. The drug, properly diluted so as to make a volume of 0.5 to 1 c.c., is injected into the anterior lymph sac by means of a glass pipette. Shortly before the hour is up the frog is pithed, tied to a frog board, and the heart is exposed in the usual manner. If the heart is still beating, the dose has been too small and must be increased in subsequent trials. In the first series doses are chosen with wide limits, which in a second and third series of animals are narrowed down until the smallest amount of the drug which will produce systolic standstill in one hour is found. Usually three series of frogs are sufficient to assay one preparation, but in case of any irregularity in the reaction of any of the frogs a fourth or even a fifth series may be necessary."

The method of Focke<sup>17</sup> is long and complicated and does not appear to have any advantage over the other frog methods that have been described.

### GUINEA PIG METHOD.

Reed and Vanderkleed<sup>20</sup> first advocated the advantages of using the guinea pig as the test animal although Houghton<sup>13</sup> had previously tried pigs but considered the frog test more reliable.

The closer biologic relation of the guinea pig to man appears to be one important reason for preferring guinea pigs. It is claimed<sup>21</sup> that "frogs not only show the pharmacological action of the drug under test, but they react with so near an approach to uniformity that the medicinal value of a tested specimen can be gauged by the determination of the minimum fatal dose—for the slowing of the heart beat and the systolic emphasis produced by active heart tonics are directly proportioned to the quantity of the drug administered, and under progressive doses at last reach a point which is incompatible with life."

#### DETAILS OF REED AND VANDERKLEED METHOD FOR TESTING DIGITALIS AND ITS PREPARATIONS.

If Digitalis leaves are to be tested a tincture is first prepared from the sample by the U. S. P. process.

An amount of any alcoholic preparation representing one-tenth of a gramme of Digitalis Leaves is placed in a very small watch glass and the excess of alcohol evaporated from it at room temperature by placing the vessel in a current of air. This residue is then carefully washed into a Hitchen's syringe<sup>22</sup> with sufficient physiological salt solution to make the total volume two cubic centimetres.

The hypodermatic needle is previously sealed with sufficient petrolatum to prevent loss of this solution.

Two cubic centimetres of physiological salt solution is placed in the side-arm of the syringe and the needle inserted under the skin of a guinea pig weighing about 250 gm.

The solution of the drug is then injected and the last portions washed under the skin with the physiological salt solution which was placed in the side arm, without removing the needle.

Great precaution is taken to inject accurate amounts and always a total of four cubic centimetres of liquid (2 c.c. of solution of drug and 2 c.c. of physiological salt).

After the injection, the guinea pig is kept under close observation and evidences and time of salivation, purgation and convulsions noted. If the pig should not develop these symptoms and die within two hours, another pig is injected with a larger quantity of the drug.

The tests are repeated until the amount of the drug is found which will produce the characteristic symptoms of *Digitalis* poisoning and kill a 250 gm. guinea pig in two hours.

Post-mortem examinations are always made to note the condition of the heart and dilation of the blood-vessels.

In testing solid preparations of *Digitalis* a weighed quantity of the preparation is shaken with a definite amount of physiological salt solution so that two cubic centimetres of the liquid will represent one-tenth gramme of the drug. This method has been found quite satisfactory, but Pittinger<sup>23</sup> has found that more concordant results are obtained if the time of observation is extended from two hours to twenty-four hours. One disadvantage to the method is that the cost of the required pigs is usually greater than the frogs necessary for Houghton's method. This objection is largely overcome by manufacturers of antitoxin who can use the pigs that have survived the antitoxin tests for digitalis tests. These pigs cannot again be used for testing serum on account of anaphylaxis, and by the time they have completely recovered from the antitoxin tests they may weigh much more than 250 gm., which is the weight specified. No provision is made for the varying susceptibility of the pigs and it is doubtful if the pig test, as it is usually carried out, will give any more reliable results than a larger number of frogs that have been "standardized" with crystalline strophanthin.

#### THE CAT METHOD OF HATCHER AND BRODIE.<sup>24</sup>

This method is based upon the determination of the minimum lethal dose for cats. The cat is anæsthetized with ether and about one-half of the amount of the preparation being tested necessary to kill the animal is injected directly into the venous circulation. The originators of this test have found that if preparations of digitalis or other members of this series are injected until the cat dies, the results will usually be too high, hence, after twenty minutes a 1 to 100,000 solution of Merck's Ouabain is cautiously injected until the cat shows signs of dying, namely, rapid respiration, which soon becomes irregular and is accompanied by convulsive movements. The Ouabain should be injected in such amounts that the cat should die ninety minutes after the beginning of the test.

The "cat unit" is the amount of crystalline Merck's Ouabain which is fatal within about ninety minutes to each kilogram body

weight of the cat. This amounts to 0.1 milligramme of the Ouabain and the number of "cat units" in one cubic centimetre of the preparation being tested is computed from the data obtained. Eckler<sup>25</sup> has reported serious disadvantages to this method, and it is doubtful if it will ever have the popular favor the other two methods enjoy.

#### FACTORS RELATING TO THE STANDARDIZATION OF DIGITALIS.

It may easily be seen that the last word has not been said in regard to the standardization of Digitalis and this unsettled condition, in its standardization, is certain to prevail until the therapeutic uses and chemistry of the drug are agreed upon.

It is true that some fault can be found with the methods we have outlined and no doubt many factors will soon be eliminated.

At the present time, it is possible to determine by physiological tests with reasonable accuracy the variability of the crude drug, the stability of its preparations, and to prepare preparations of considerable uniformity.<sup>26</sup>

#### OTHER HEART TONICS.

What has been said in regard to the methods used for standardizing Digitalis applies also to preparations of Strophanthus, Squill and Convallaria. Strophanthus seems to be more certain in its action than digitalis and can also be advantageously tested by the blood-pressure method upon dogs.

*Cactus grandiflorus* has long been used empirically with apparently favorable results, yet competent pharmacologists have reported that it has no action analogous to digitalis<sup>27,28</sup>. Graeber<sup>29</sup> has recently reported the presence of both alkaloids and glucosides in this drug and publishes experiments on frogs which "indicate that *Cactus grandiflorus* actually is possessed of an action upon the heart such as belongs to the substances of the digitalis group." In all his frog experiments the frequency of the pulse was reduced and the systole strengthened.

Sparteine sulphate is considered a drug of mediocre importance as a "heart tonic," yet Pettey<sup>30</sup> considers that Sparteine is unappreciated because it is not given in sufficient doses. He recommends the use of 2 grain doses as a true and reliable heart tonic, an excellent non-irritating diuretic and states that this dose is entirely free from untoward or objectionable effects.

## WORK OF THE NORMAL HEART.

Few realize the vast amount of work performed each day by the heart of the normal adult. One-fifth the total muscular energy of the body is used in propelling the heart and about twelve tons of blood are pumped each day.

## NEW METHODS OF OBSERVING CONDITIONS OF THE HEART.

The electro-cardiographic method<sup>31</sup> has made possible not only the accurate diagnosis of diseases of the heart but also enables the physician to observe the effects of the medicine he has prescribed. The practice of medicine under these conditions has become scientific, not empiric, and if uniform preparations of the "heart tonics" can be supplied, the physician needs only to consider the idiosyncrasy of the patient.

## SUMMARY.

In presenting this subject I have attempted to dwell not alone on the methods used in standardizing the "heart tonics" but the various factors that must be considered in producing reliable and potent preparations. The clinical side of the problem must not be lost sight of, and when a preparation is made that will produce certain therapeutic results it is of vital importance to produce another lot having the same action. Uniformity is practically as important as potency. When a competent observer like Faught<sup>32</sup> says "Usual preparations are variable and cannot be depended upon unless coming from a reliable source. I have seen less effect follow the administration of 20 minims of a poor preparation than 5 minims of a good active one" it is time to improve conditions. Conditions can be improved by the adoption of pharmacological standards and methods for these drugs. At the present time the manufacturers who have wisely adopted physiological standardization of their products often have different standards while those that have not adopted physiological standards have no assurity that these important drugs are even active.

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## COLLOIDS AND CRYSTALS, THE TWO WORLDS OF MATTER.\*

BY ROBERT H. BRADBURY,

Head of the Department of Science in the Southern High School, Philadelphia.

When a solid is brought into contact with a liquid the result depends upon the nature of both. There may be apparently an entire

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\* Presented at the meeting of the Section of Physics and Chemistry held Thursday, April 10, 1913, and reprinted from *Jour. Franklin Institute*, September, 1913.

absence of interaction, as when rosin is shaken up with water or chalk with alcohol. Or, as when sugar is agitated with water, the solid may disappear, entering into solution in the liquid. The study of sugar solution shows quite clearly that the connection of the sugar molecules with each other has been completely destroyed. They are dispersed through the water very much as the molecules of a gas distribute themselves uniformly in a vacant space, and in both cases the permanence of the uniform dispersion is due to the incessant motion of the molecules. Were the molecules at rest, both the sugar and the gas would settle and form a layer on the bottom of the containing vessel.

However, the molecules of the sugar retain their structure intact, the action being limited to their dispersion. When salt, on the other hand, is dissolved in water, a further breakdown occurs, the molecule is separated and ions of sodium and of chlorine move about in the liquid. Both solutions freeze below  $0^{\circ}$  C. and boil above  $100^{\circ}$  C. The most important difference between them is that the salt solution conducts the electric current, while the sugar solution is as poor a conductor as water itself.

A fourth possibility presents itself when glue or gelatin is treated with water. The gelatin absorbs water, swells up and, under the influence of heat, dissolves, but the liquid freezes and boils at practically the same temperatures as pure water. The study of the solution shows that the dispersion is not molecular. The particles of gelatin in it are composed of variable and rather large numbers of molecules. A system like this gelatin solution which presents a case of very fine but not molecular subdivision is called a *colloidal solution*. There are certain solids such as gelatin and dextrin (with water), and rubber (with benzene and carbon disulphide), which, when they dissolve in liquids, are invariably dispersed in this way. Such solids may properly be referred to as *colloids*. They are all amorphous. Crystallized substances never yield colloidal solutions by mere spontaneous solution in a liquid. They always produce molecular or ionic dispersions. However, the phenomenon of colloidal solution is perfectly general, and crystallized substances can also be obtained in this condition, but not by mere solution.

It is an interesting fact that a substance which yields a colloidal solution with one solvent may form an ordinary molecular solution with another. Soap is an example. Its concentrated solution in

water boils at about  $100^{\circ}$ , freezes at about  $0^{\circ}$ , and exhibits the behavior of a colloidal solution in general. On the contrary, a soap solution in alcohol shows the normal change in freezing and boiling points corresponding to the molecular weight, and conducts itself in all respects like an ordinary molecular dispersion.

## II.

Every one is familiar with the distinctions between solutions and suspensions. Suspensions are turbid in aspect, and the solid can be removed by letting it settle, or by filtration. Solutions are clear, dissolved matter does not subside and is unaffected by filtering. Colloidal solutions occupy an intermediate position.

Consider for a moment the effect of increasing subdivision on a suspension of finely-divided gold in water. So long as the diameter of the particles is much greater than a thousandth of a millimetre,<sup>1</sup> the system will be turbid and the gold will settle rapidly. But the wave-length of visible light ranges between  $0.4 \mu$  and  $0.7 \mu$ , and when the particles become smaller than this they can no longer reflect light and the liquid will appear clear. At the same time there will be a rapid falling off in the speed of settling. Stokes has derived a formula for the velocity of subsidence,  $V$ , of small spheres of radius  $R$  and density  $S$  falling in a liquid of density  $S'$  and internal friction  $f$  under the force of gravity  $g$ :

$$V = \frac{2}{9} g(S - S') \frac{R^2}{f}$$

Substituting the proper values for gold and water and assuming a radius of  $\mu$  for the particles, the value for  $V$  is about 14 centimetres per hour. This means, of course, that the system would be a coarse suspension and would clear up at once. But when  $R = 10 \mu$ ,  $V$  is only about a centimetre a month. This begins already to be fairly permanent. It must be remembered that the high density of gold (19.5) increases the rapidity of subsidence. If we make the calculation for  $S = 3$ , which is about the density of arsenious sulphide,  $V$  comes out only about a millimetre a month.

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<sup>1</sup> It is usual to employ the symbol  $\mu$  (the Greek letter mu) for the thousandth of a millimetre. In the same way  $\mu \mu$  indicates the millionth of a millimetre.

So much for calculation. Now what are the facts? As a matter of fact, the dispersed substance in a colloidal solution does not settle at all, so long as the subdivision is maintained. Colloidal gold solutions have been preserved unchanged for years. I have a solution of arsenious sulphide which has remained apparently unchanged for three years and whose countless particles can readily be seen, engaged in their incessant Brownian movement, with an ordinary oil immersion lens. Whenever settling does occur, it is preceded by the aggregation of the particles into larger particles, which finally attain a diameter of  $\mu$  or over, and slowly subside.

Here, then, is an apparent discrepancy between Stokes' law and the facts. The law informs us that the speed of subsidence decreases rapidly with decreasing radius of the particles, but it does not lead us to expect the total absence of settling which presents itself when the average radius is  $10 \mu$  or thereabout.

The explanation, of course, is molecular motion, or, in other words, *heat*. The particles are battered, on all sides, by a hail-storm of molecular impacts. If the particle is large, the blows of the molecules of the solvent in different directions neutralize each other. But when the particle is not so very much larger than the molecules themselves a molecule striking, say on the left, will give the particle a very perceptible push toward the right, "just as a cork follows better than a large ship the motion of the waves of the sea."<sup>2</sup> As the dimensions of the particle approach the molecular dimensions it begins to behave like a molecule and is swept along in the endless molecular movement. The cause which prevents the particles in a colloidal solution from settling is in no way different from the cause which prevents the earth's atmosphere from subsiding to a snowy layer a few feet deep on the surface of the planet.

It is worth remembering, also, that the particles of the dispersed phase ordinarily possess an electric charge, which is usually negative. The effect of the repulsion of these similar charges would be to preserve the distribution of the particles throughout the liquid. It is a fact that, when the charges are removed, the system becomes instable and subsidence—preceded by coalescence of the small particles—readily, but not necessarily, occurs.

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<sup>2</sup> Perrin.

## III.

On the subject of the classification of colloid systems we must be very brief. One proposal subdivides them into *suspensoids*, such as the sols<sup>3</sup> of gold and arsenious sulphide, in which the dispersed phase is solid, and *emulsoids*, in which the dispersed phase is liquid. This classification would appear to be an attempt to extend the familiar distinction between liquid and solid to a domain in which that distinction has little if any meaning. To assert that a thing is solid is to say that it has a definite shape, which it retains with some persistence. There is not the slightest reason to think that the particles in a gold sol are solid. It is usual to assume that they are spherical, but this is done merely because it is the simplest assumption to make. There are faint indications that they really have the form of leaflets or of little rods, but they appear in the ultra-microscope simply as brilliant dancing points, and in reality we know nothing whatever about their shape. In connection with this it is interesting to recall the fact that the formation of a crystal begins with the appearance of minute liquid spheres (globulites),<sup>4</sup> which pass through several stages (margarites, longulites, etc.) before the crystal is formed. It seems possible that, under such enormous subdivision, cohesion retires into the background and surface tension assumes the chief rôle, so that the gold particles are rather to be compared to minute drops than to little crystals.

Enough has been said to make clear the uncertainty which attaches to the attempt to classify colloid solutions according to the state of aggregation of the particles. A better classification is into *reversible* and *irreversible* colloids, according to the way in which the dissolved substance behaves when separated from the solution. Thus, when a gelatin solution is evaporated until it "sets" it is only necessary to warm the jelly with water to obtain it again in colloid solution. Gelatin is a typical reversible colloid. But when the gold is caused to separate from a gold sol—which can easily be brought about by adding any electrolyte to the sol—the gold will not again enter into colloidal solution. Shaking or warming with water gives a mere

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<sup>3</sup> Thomas Graham introduced the term sol as an abbreviation for colloidal solution.

<sup>4</sup> Fink, "Poggendorff's Annalen," vol. 46, p. 258 (1839); Schmidt, "Liebig's Annalen der Chemie," vol. 53, p. 171 (1845); Frankenheim, "Poggendorff's Annalen," vol. III, p. 1 (1860).

suspension, which settles at once. Gold is an *irreversible* colloid. The distinction is fundamental. Many organic colloids are reversible, while it is rather the habit of the inorganic colloids to behave in the irreversible way.

#### IV.

In order to prepare a sol containing an irreversible colloid all that is necessary is to reduce the solid to extreme subdivision in a liquid in which it is insoluble. The electric arc furnishes a rapid and simple method.<sup>5</sup> Two gold wires about 2 mm. thick are connected with a 220-volt circuit and brought together under distilled water. A 110-volt circuit can be used, but more patience is required. Sols of platinum, silver, copper, and other metals can be made in the same way. By related electrical methods, using such liquids as pentane and anhydrous ether, Svedberg<sup>6</sup> obtained sols of all five of the alkali metals. The colors of the sols agreed with those of the vapors of the corresponding metals.

Chemical reduction of a salt of a metal furnishes another method which has been largely employed by Zsigmondy<sup>7</sup> and other investigators. For instance, a very dilute solution of auric chloride is mixed with such reducing agents as formaldehyde, hydroxylamine or an ethereal solution of phosphorus. The gold sols obtained in this way are usually red by transmitted light, the particles being bright green and very much smaller than in the sols obtained by the electrical method.

By various chemical methods, which lack of space forbids us to discuss, sols of sulphides ( $\text{CdS}$ ,  $\text{As}_2\text{S}_3$ ,  $\text{Sb}_2\text{S}_3$ , etc.) and oxides ( $\text{Fe}_2\text{O}_3$ ,  $\text{Al}_2\text{O}_3$ ) can be obtained. The sol of aluminum oxide is important on account of its connection with dyeing and mordanting. The formation of the blood-red sol of ferric oxide by adding a concentrated solution of ferric chloride to about 50 volumes of boiling distilled water is a simple and beautiful lecture experiment.

In making colloidal solutions of *salts*, the essential thing is to mix dilute solutions of the precipitants, using a liquid in which the

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<sup>5</sup> Bredig, *Zeitschrift für angewandte Chemie*, 1898, p. 951. For a full account of Bredig's work with the platinum sol see *Zeitschrift für physikalische Chemie*, vol. 31, pp. 258-353 (1899).

<sup>6</sup> *Berichte der deutschen chemischen Gesellschaft*, vol. 38, p. 3616 (1905).

<sup>7</sup> See his monograph, "Zur Erkenntniss der Kolloide" (Jena, 1905), which has been translated by Jerome Alexander.

insolubility of the product is as complete as possible. Thus, in mixing very dilute solutions of sodium sulphate and barium chloride, a crystalline precipitate is usually obtained. The reason is that barium sulphate possesses a very slight but real solubility in water. Hence the liquid in contact with the particles first formed contains enough barium sulphate to nourish their growth and allow them to develop to crystals. If alcohol is added to the sulphate, before the barium chloride is introduced, the solubility of the barium sulphate is greatly reduced, and it is obtained in colloidal solution without difficulty.

In the same way, if we mix water solutions of sodium hydroxide and of hydrochloric acid we obtain merely an ordinary solution of common salt. But if salt is produced by a reaction between organic compounds in a liquid in which the sodium chloride is insoluble, then a colloidal solution is obtained. For instance, when chlor-acetic ester interacts with sodio-malonic ester a grayish opalescent sol of sodium chloride in ethenyl tri-carboxylic ester results:  $\text{CH}_2\text{Cl COOC}_2\text{H}_5 + \text{CHNa}(\text{COOC}_2\text{H}_5)_2 = \text{CH}_2(\text{COOC}_2\text{H}_5) - \text{CH}(\text{COOC}_2\text{H}_5)_2 + \text{NaCl}$ . At low temperatures, in such liquids as toluene and chloroform, even *ice* has been obtained in colloidal solution.

## V.

The most striking property of the reversible colloids is that they are able to communicate their reversibility to the irreversible ones. Thus, if a trace of gelatin is added to a gold solution, the gold becomes much more difficult to coagulate by electrolytes, and when coagulated it can be dispersed again by merely warming with water. This curious protective action is exerted, in greatly varying degree, by most reversible colloids. Direct study of the phenomenon with the ultra-microscope shows that the view frequently expressed that the gelatin envelops or forms a film around the gold particles is incorrect. What actually happens seems to be a direct combination between gelatin particles and gold particles, which then pass through the reversible changes together.

Protective colloids enjoy a wide practical application. In the manufacture of photographic films the gelatin retards the crystallization of the silver bromide. Ink often contains a colloid which prevents the pigment from settling. The lubricant "aqua dag" put in the market by the Acheson Company consists of finely-divided artificial graphite, held up by a protective colloid. Clay is made plastic

for the potter by an empirical process which involves the action of protective colloids derived from decaying vegetable matter. The addition of gelatin in making ice cream depends upon its protective action in preventing the growth of ice crystals, which would make the product "gritty." Without doubt protective action plays an important rôle in the cleansing action of soap. This has been made clear by some recent experiments of Spring.<sup>5</sup> Lampblack, freed from oil by long washing with alcohol, ether, and benzene, forms a rather stable suspension in water, but the lampblack is detained by a paper filter. If the filter is now reversed, so that the blackened surface is outward, and water poured through it, the lampblack is not removed, but a dilute soap solution removes the coating and cleanses the filter at once. Finally, lampblack suspended—or colloidally dissolved—in soap solution, passes through a filter unchanged. It is of much practical interest that there is a well-marked optimum in the concentration of the soap required to protect the lampblack. A one per cent. soap solution is the most efficient. In two per cent. soap solution lampblack sinks about as rapidly as in pure water.

## VI.

We have already considered the probable actual condition of the particles in a colloidal solution and have concluded that, for the present, no very definite information is obtainable about the matter. We must now return, for a moment, to the subject in order to allude to the thesis so brilliantly advocated by van Weimarn, the Russian investigator, who holds that the particles are of necessity minute crystals and that there is, in fact, no such thing as amorphous matter. He even goes so far as to state that substances like air and water are in a "dynamic crypto-crystalline condition," though I have been unable to understand what he means by this statement.

Briefly, the evidence that van Weimarn adduces to the support of his hypothesis is:

(1) That colloid particles will grow to crystals if provided with the proper nourishment, namely, a dilute solution of the same substance.

(2) That colloid particles are capable, when introduced into

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<sup>5</sup> *Kolloid Zeitschrift*, vol. 4, p. 161 (1909); *Kolloid Zeitschrift*, vol. 6, pp. 11, 109, 164 (1910).



a supersaturated solution of the same substance, of discharging the supersaturation and inducing the formation of crystals.

Those who desire to follow this matter further should read van Weimarn's little book, "Grundzüge der Dispersoidchemie," after which they will find themselves very much interested, but somewhat unconvinced. Let me hasten to add that I have not the least desire to undervalue the brilliant experimental work of the Russian chemist. It is, in fact, precisely by the conception of more or less daring hypotheses, and the working out of their consequences, that our science achieves its endless victory over the nescience about us.

## VII.

We have seen that the wave-lengths of the visible radiations are comprised between  $0.4 \mu$  and  $0.7 \mu$ . With objects much smaller, the ordinary microscopic method ceases to be applicable. Using ultra-violet radiation for illumination, quartz lenses in the microscope, and receiving the image with the photographic plate instead of the eye, it is possible to advance a step further in the domain of the infinitesimal, but only a step, and there are obvious objections to the proceeding. Since some of the particles in colloidal solutions are only  $0.006 \mu$  in diameter, we can never hope to see them as little bodies subtending a visual angle. The *ultra-microscope*—the powerful instrument of investigation to which most of our knowledge of colloid systems is due—renounces this idea and makes the particles visible merely as glittering points on a black background. The sol is placed in a small rectangular glass trough and a horizontal beam of arc light or sunlight focussed in it. The microscope is placed vertically above the trough. It will at once be seen that there are two fundamental things about the instrument: to provide intense illumination, and to make sure that no light enters the microscope except the rays which emanate from the particles. The principle is simple, but the system of diaphragms and lenses needed to secure the second object makes the ultra-microscope an elaborate and expensive instrument in practice.

Cotton and Mouton<sup>9</sup> achieve the same end in a different way. The illumination (arc or sunlight) is thrown up from below by a paraboloid reflector so ground that all rays, *except those diffracted*

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<sup>9</sup> *Compt. Rendus*, vol. 136, p. 1657 (1903).

by the particles, are totally reflected from the cover-glass over the sol. This instrument is simple, easily adjusted and cheap. It is made commercially by the firm of Zeiss. It would seem to be admirably adapted to school purposes. In fact, after a look into the ultra-microscope, the study of the molecular topics ceases to be drudgery and becomes a positive intellectual need.

### VIII.

Even a brief glance at the subject of colloid systems must at least mention the classic work of Perrin<sup>10</sup> on the distribution of the particles in suspensions of gamboge and mastic. He succeeded, by an ingenious and simple method, in preparing emulsions of gamboge in water in which the spherical yellow granules were all of the same diameter. If we consider a mass of such a liquid in a tube, it is clear that the granules, if at rest, would, since they are denser than water, all fall to the bottom. The fact that they remain suspended is due to their movement. In other words, the state of things is the same as in the earth's atmosphere, and just as the molecules are more crowded near the earth's surface, so the granules of gamboge must be more numerous near the bottom of the liquid than in the upper layers. Perrin verified this prediction by direct counting of the granules under the microscope. The barometric formula which describes the progressive rarefaction of air with increasing height also describes the distribution of the granules in Perrin's uniform emulsions. The only difference is that, while the aviator must ascend six kilometres in order to reach air half as dense as at sea level, the same effect is produced, in Perrin's emulsion, by an ascent of 0.1 millimetre.

That the mean energy of rotation of a molecule must be equal to its mean energy of translation is one of the chief propositions of the kinetic theory. Perrin has proved this by direct measurement of the rotation of granules under the microscope. For this purpose, large granules ( $15\ \mu$ ) of mastic were employed. These are far too heavy to remain suspended in water, so a solution of urea was used. Fortunately, the granules contain little inclusions which make it possible to measure their rotation.

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<sup>10</sup> *Annales de Chimie et de Physique*, 3d series, vol. 18, p. 5 (1909). There is a German translation by Donau in *Kolloidchemische Beihefte*, vol. 1, p. 1 (1910). An English translation by Soddy has appeared in book form under the title "The Brownian Movement and Molecular Reality."

These are only two of many fundamental results contained in this wonderful memoir. Van't Hoff extended the gas laws to solutions. Perrin has now proved them to be valid for systems in which the moving particles are visible realities. Let us end by quoting one of the sentences of his conclusion:

*"La découverte de telles relations marque le point où s'élève, dans notre conscience scientifique, la réalité moléculaire sousjacente."*

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## THE INFLUENCE OF HEAT AND CHEMICALS ON THE STARCH GRAIN.<sup>1</sup>

BY HENRY KRAEMER.

In presenting some of the most recent observations on the starch grain, it may be well to consider for a moment the nature and origin of starch. In a way starch is one of the most remarkable substances produced by the plant. It is the first visible product formed by the chloroplastid, or chlorophyll bodies, from the inorganic substances, carbon dioxide and water. Inasmuch as sunlight seems to be necessary to bring about this transformation the process is looked upon as one which involves the converting of the sun's energy into vital energy.

The substance thus formed by the chloroplastid through the influence of sunlight, in the leaves and other green parts of plants, is known as "assimilation starch," and serves subsequently not only as a food for the plant itself but is also the source of the energy of the animal world. Assimilation starch is not stored in the cells where it is manufactured, but each night through the influence of the plant ferments the starch formed during the day is converted into a soluble form, and transported to various other parts of the plant. In some cases this soluble starch is temporarily stored in the cells of the pith, medullary rays, or bark, and has received the name of "depot starch." While some of the soluble carbohydrate is converted into fixed oils and other substances, a considerable portion of it is carried to some reserve organ, as a root, tuber, rhizome, or seed, and under the influence of a plastid similar to the chloroplastid, converted into a stable form, known as *reserve starch*.

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<sup>1</sup>Reprinted from Original Communications, Eighth International Congress of Applied Chemistry. Vol. XVII—Page 31.

This is the product with which we are specially concerned in the present article. Heretofore, the minute study of the starch grain, particularly of its structure, has been of scientific interest only, but with the application of scientific methods in nearly every department of industry, it is coming to have a practical application.

The commercial reserve starches are derived from various plants, and not only enter largely into food products but are also used for a variety of technical purposes. The grains of the reserve starches have a number of characteristic features. They vary in size, in shape, in internal structure, and also to a considerable extent in composition. The variation in composition is shown by the use of aniline stain and also by the use of iodine. By the treatment of starch with iodine solution, we may distinguish three kinds of reserve starch: (1) one which is colored deep blue, as potato and maranta; (2) one which is colored somewhat purplish, changing to cinnamon-brown, as corn and wheat; and (3) one which is colored brownish-red, as in the amylo-dextrin starches of comfrey and a few other plants.

The shape of the grains varies from polygonal to ellipsoidal, the shape being influenced by the number of grains in a cell. Under the micro-polariscope the grains are seen to be anisotropic, the polarization effects differing with the grains of the different classes. Polarizing effects are usually produced by crystals, but may be produced by substances in a condition of tension, as minute globules of glass. It should also be stated that cell walls have this same property of double refraction, and it is very likely that the substances in the starch grains, as well as in the cell wall, are crystalloidal and arranged in spherite aggregates, resembling those of inulin, a product closely resembling starch.

The theories which have been advanced regarding the structure of the starch grain, have been largely based on studies of the potato starch grain. It was originally thought to be in the nature of a globule filled with a fluid. Fritzche, Schleiden and others considered it to be made up of more or less concentric layers formed around a central or excentral point. While it may be true, as pointed out by Naegeli, that many of the reserve and glucose starch grains arise free in the cell, the view of Schimper that starch grains always develop within plastids, is generally accepted at the present time.

The internal structure of the starch grain is shown in several

ways. When starch is treated with certain chemicals, or heated with water alone to a temperature of  $60^{\circ}$  C., the grains show a series of successive changes. First, the lamellæ or layers become more distinct, and the layers appear to be made up of parallel crystal-like particles, these latter being more numerous in successive alternate lamellæ. Then as the grain swells clefts which radiate from the centre are formed. Later the centre of the grain becomes hollow, and when the grain has swollen to about four times its original size the outer membrane breaks and the contents are gradually dissolved.

Some striking effects are also produced when starch is carefully treated with aniline dyes. The point of origin of growth and the successive layers alternating with it take up the stains, thus again showing the distinct character of the two kinds of lamellæ making up the grains. When plant material containing mucilage is treated with aniline stains, the stain is taken up only by the cells containing mucilage, and this indicates that the lamellæ in a starch grain which take up the stains are composed chiefly of colloidal substances. From these observations it is apparent that the grains of certain of the starches, as the potato, if not of all the lamellated starch grains, are made up of two kinds of lamellæ, one rich in colloids and one rich in crystalloids. The presence of two kinds of lamellæ, at least in certain of the starch grains, and their difference of composition are further shown by the use of a weak solution of iodine, the so-called crystalloidal layers or lamellæ taking up the iodine and becoming blue.<sup>2</sup>

Recently I have been conducting some experiments to determine further the effects of heat upon the structure of the starch grain. When starch alone is heated to between  $45^{\circ}$  and  $50^{\circ}$  C. from 15 to 30 minutes, the lamellæ and the crystalloidal structure of the grains are brought out. The grain is so resistant that the inner structure does not appear to be lost until a temperature of over  $125^{\circ}$  C. is attained. Between  $140^{\circ}$  and  $160^{\circ}$  C. the polarization effects of the grains become faint, except in the case of potato starch, which now in addition gives chromatic effects. At  $240^{\circ}$  C. all of the grains are disintegrated except those of corn starch, the individual grains of which are of a brownish-yellow color and not perceptibly

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<sup>2</sup> Kraemer, *Bot. Gazette*, Vol. XXXIV, Nov., 1902; *Ibid.*, Vol. XL, Oct., 1905; reprinted in *Amer. Jour. Pharm.*, Vol. 79, 1907, pp. 217-229; 412-418.

swollen. Besides the entire mass is more or less granular, while in the case of the other starches examined the charred mass is in a puffed condition.

The effects produced when starch is heated in the presence of a fixed oil, as almond oil, are of special interest. The inner structure of the starch grain is not usually apparent when it is mounted in a fixed oil, unless the starch has been previously heated to a temperature of from  $80^{\circ}$  to  $160^{\circ}$  C. When, however, a mixture of starch and oil is heated as high as  $180^{\circ}$  C. the grains still polarize light, which shows that the structure has not been altered. In other words the effects of heat on the grain are more or less neutralized by the presence of the oil. On heating the mixture up to  $250^{\circ}$  C. most of the grains still show their individual character, but no longer polarize light. They are but slightly swollen, and in the case of cassava and corn starch a central differential area occupies from one-half to nine-tenths of the original area of the grain.

It may be worth while to state that when starch and water in the proportion of 2 gm. of the former to 100 c.c. of the latter, are heated together at a temperature of between  $90^{\circ}$  and  $100^{\circ}$  C. in a steam sterilizer seven or eight hours a day for a long period, even extending to months, dextrinization of the starch does not take place, that is, the solution still gives a blue color with iodine. Even though the operation be conducted in an autoclave under a pressure of 20 pounds for about ten hours, dextrinization is not effected. If, however, 1 c.c. of  $N/HCl$  be added to 100 c.c. of water and this heated for five hours with 1 gm. of starch, the resulting solution is colored red with iodine. When the amount of the acid is reduced to .2 c.c. and the mixture heated under a pressure up to 12 pounds for one hour, cassava, corn, maranta and potato starch solutions give a deep blue color with iodine, while a solution of wheat starch gives a deep purple color with iodine. If the heat be continued an hour longer, wheat starch gives a purplish-red color, cassava a deep wine color, maranta and potato a light purple, while corn still gives a blue reaction with iodine.

These observations may be summarized as follows:

1. The starch grain consists of two nearly related substances:  
(a) a colloidal or mucilage-like substance which takes up aniline

dyes, and (b) a crystalloidal or crystal-like material giving a blue color with iodine.

2. The starch grain is made up of concentric layers, one series of which contains a large proportion of crystalloids, while the alternate layers are composed mostly of colloids.

3. The polarization effects produced by starch are probably to be attributed to the crystalloidal character of the grains.

4. The starch grains retain their polarizing properties even when heated up to a temperature of  $180^{\circ}$  C., which seems very remarkable indeed.

5. At the higher temperatures the potato starch grains give chromatic effects in addition, similar to those when a selenite plate is used.

6. While heating the starch grains in water rapidly changes the structure of the grain, it is only by the addition of chemicals or ferments that dextrinization is brought about.

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## BOOK REVIEWS.

SEMI-ANNUAL REPORT ON ESSENTIAL OILS, SYNTHETIC PERFUMES, &C. Published by Schimmel & Co. (Fritzsche Brothers), Miltitz near Leipzig. London, New York. October, 1913.

In the introduction to this report an admirable résumé is given of conditions, both favorable and adverse, which affected business in the last year and particularly as to commodities handled by this firm.

As is known to well-informed pharmacists, the practice of sophistication is found in many branches of business but in none so much as in the essential oil industry. In fact, one is almost led to believe that adulteration of oils and perfumes is an industry in itself. Upward movement of prices is the dominant cause for this, and, as is always the way, the forces of evil and dishonesty are up and doing, and "the practice of adulteration is assuming dimensions, and is pursued with refinements of ingenuity that baffle description." So cleverly are adulterants selected and manipulated that the constants of an adulterated oil are kept within the right limits of value and only a most thorough examination will show the true state of affairs. Artificial esters play an important part in this nefarious work; for instance, when added to oils such as lavender

and bergamot, they give "to them the appearance of containing far more linalyl acetate than the oils possess in reality."

In this report the statement is made that there are firms who do not hesitate to offer such esters openly for purposes of adulteration. Furthermore, it is stated that one firm made such an offer to the Schimmel people in writing who publish this communication in the original language and a translation of which follows:

GENTLEMEN:

For some years past we have been in the habit of supplying to lavender growers a product called "Ether L."

The advantage of this article is that it simulates in a perfect manner essential oil of lavender, and we have judged it opportune to forward you to-day a sample of it by post. The price is 12.50 francs per kilo delivered at your works.

• If this product should interest you by any chance, please let us know what quantities of it you would be able to use annually.

Hoping to hear from you we are, &c.,

N. V. Polak & Schwarz's,  
Essence Fabrieken,  
Zaandam (Holland).

P. S.—Our Ether L. is pure and contains 100 p. c.

Subsequent examination of this product showed that instead of being 100 per cent. it revealed a percentage of 86. The presence of this ester in lavender oil would not prove difficult of detection.

The high price of menthol also proved a stimulus to those of dishonest tendencies. Two samples examined showed 100 per cent. adulteration. Both were acetanilid, one scented with menthol and the other with peppermint oil. Under the name Mentholin there is being offered to the trade a substitute for menthol made by a firm in Prague which proved to be 80 per cent. acetanilid and oily menthol.

This report consists of 151 pages of interesting matter, the greater part of which is devoted to commercial notes and scientific information pertaining to essential oils; practically every oil used in pharmacy and in the manufacture of perfumery is touched upon as to source of production, supply, and conditions, favorable and otherwise, which may have had some influence on quality or lack of quality.

Considerable attention is given to recent scientific research in



the field of essential oils. Abstracts of reports on experimental cultivation of medicinal plants are given, a field of endeavor which must be nurtured if the supply of drugs is to keep pace with the demand.

Among the pages of this report are several excellent pictures illustrative of the essential oil industry. One is a particularly striking view, in color, of the Miltitz rose-fields at harvest time.

After reading over this report and digesting the information given, one cannot help but feel that in the examination of an oil (say oil of rose) and in which the other constants are normal—a remarkably high ester value should be regarded with suspicion!

BRITISH PHARMACEUTICAL CONFERENCE. A PRESIDENTIAL SURVEY 1863 TO 1913. Being a sketch of the origin and progress of the conference prepared on the occasion of the celebration of its jubilee in London, July 21 to 25, 1913. The Chemist and Druggist, 42 Cannon Street, London.

This handy little volume of 96 pages contains concise but interesting biographies of the various men who have been honored by the presidency of the British Pharmaceutical Conference.

In the fifty years of its existence the Conference has been guided by thirty-three presidents, all men of ability and some of rare scientific attainments. Among the list of names two stand out in bold relief—Hanbury and Attfield. These two names are probably more familiar to workers in pharmacy in this country than any other two from other lands. Hanbury won an enviable position in the world of science by his work as a pharmacognocist. He will also be remembered as the donor of the Hanbury Medal. This is only given to men who have *done* something and our own Professor Maisch was the first American to receive this signal honor. And Attfield, we think few American students are unfamiliar with the book on chemistry bearing that name, with its many chemical experiments which the student is advised to perform. He impressed on the student the fact that the way to study chemistry was to work at it.

JOHN K. THUM.

PAYNE'S DICTIONARY OF PHARMACY. By George F. Payne, Ph.G., M.D., F.C.S. Published by G. F. Payne, Atlanta, Ga.

Lack of space forbids us to give the full title given by the author to this little handbook of pharmaceutical facts. For the same

reason we are compelled to omit mention of the numerous offices and honors the distinguished writer has been honored with and which he mentions on page one. It suffices to say that he is "an active pharmacist for 51 years"; that the little volume is copyrighted, and all rights are reserved, whatever that may mean.

We have been rather hopeful that the day of cramming books was over, but this short-cut to the study of pharmacy and allied branches seems like evidence to the contrary.

The study of a science and art like pharmacy by the "absorption" of isolated facts is a survival of the day when the unschooled errand boy of the retail drug store developed into a clerk and squeezed through a board of pharmacy examination by heroically attempting to memorize the dispensatory. In the past, board of pharmacy examinations consisted very much of "catch" questions and a student expected them and prepared for them; if he answered them correctly the board assumed that he was fit to practise pharmacy; all of which was not conducive to the best interests of the public and certainly lowered the level of the profession. Indeed, the inefficiency of many pharmacists, who must, because of such inefficiency, depend upon manufacturing houses for many pharmaceuticals that they should make themselves, can be traced to this method of education or lack of education in their chosen profession.

Happily, in the larger centres of our country there is beginning to manifest itself by the public a demand for a higher type of man for the professions, ours included. And this demand is being met and complied with by the better class of schools with more stringent requirements as to preliminary education and a broadening of the curriculum. This is as it should be, and in the evolution of things schools of other centres must do likewise or cease to exist.

JOHN K. THUM.

MATERIA MEDICA, PHARMACOLOGY, THERAPEUTICS, PRESCRIPTION WRITING, FOR STUDENTS AND PRACTITIONERS. By Walter A. Bastedo, Associate in Pharmacology and Therapeutics at Columbia University, etc.

This book, which is from the press of the W. B. Saunders Co., is a medium 8vo. in size, of 602 pages, price \$3.50 net. It is an excellent specimen of the book-making art, the binding and paper being excellent, the type clear and distinct.

The work is original in many respects, not following the beaten path, and has in it much to commend.

It is divided into three parts, Part I being largely by way of introduction. Among some of the subjects considered in this division are: Pharmaceutical preparations; Weights and measures; Active principles; The Pharmacopœia; Dosage, Administration of medicines, etc.

Part II treats of *materia medica* proper. Many of the classifications are different from other books on this subject, one of them being Sweetening Agents, which includes saccharin, which he states "has been much employed in canning foods, as it is slightly antiseptic and obviates the use of the highly fermentable sugar." This seems to be flying directly in the face of Dr. Wiley. The Anti-Bitters are claimed to abolish the appreciation of bitter tastes; these include yerba santa and gymnemic acid. The list of cathartics include those which act by "selective affinity," as physostigmine, which stimulates the ends of the vagus nerves of the intestines. A new classification is given to the Antispasmodics, they being called the Antihysterics.

The classification of the Antipyretics is somewhat original. We have the analgesic antipyretics, such as antipyrin, the antimalarial antipyretics, such as cinchona; and the antirheumatic antipyretics, such as salicylic acid.

The article on the thyroid gland is interesting and of value, a new classification being called the Antithyroid preparations, designed to overcome undue activity of the thyroid gland, the remedies included under this head being Beebe's serum; Antithyroidin (Moebius), and Thyroidectin. Antithyroidin is the blood serum obtained from sheep whose thyroid glands have been removed, at least six weeks before.

The therapeutic classification of the Disinfectants is also original and valuable. It includes I, The general disinfectants and deodorizers; II, The preservatives; III, Disinfectants for surgical supplies; IV, Disinfectants for local use about the body; V, Disinfectants to be given by the mouth. The important drugs of the *materia medica* are treated of at considerable length, digitalis having 42 pages assigned to it, and epinephrine (adrenalin) ten pages. In the article on digitalis, it is stated that "digitalis contains digitonin, a saponin body which foams with water and possesses the peculiar property of holding the otherwise insoluble active principles in solution in water. It is on account of this that infusion of digitalis, an

aqueous preparation, represents the activity of the drug." While this is somewhat different from what we have heretofore believed, it does not justify the making of the infusion from a fluidextract, as digitonin is not soluble in an alcoholic menstruum, and such an infusion would not contain any digitonin, and the glucosides insoluble in water would not therefore be held in solution.

The book is up-to-date in the introduction of new remedies, a few only being cited, such as Hormonal from the spleen of the rabbit, which is stated to be "of value in post-operative tympanites and obstinate chronic constipation." Oxyntin and Acidol are albuminous forms of hydrochloric acid. The chapter on Hypnotics is of interest, especially the contrast between natural sleep and that induced by the aid of drugs.

The article on tobacco will be read with interest, as the author seems to think "that the demand for tobacco is not so much the physiological demand of the body for its dose of nicotine, as it is the psychic demand for the satisfaction of a habit."

He thinks that pepsin "in almost all cases of digestive disturbance is a superfluous remedy," but that pancreatin is of greater value. In fact, he gives some remarkable instances of its effects in the case of arrested development, one of which was a boy who grew five inches in two years and gained twenty-two pounds. He is opposed to the prescribing of mixtures of the digestive ferments together, as frequently they destroy each other. Of aconite which has been the sheet anchor of Homeopathy for so many years, is asserted, "that in the light of recent research has doubtful therapeutic value." Camphor cerate is not "camphor ice" as stated, the latter being the Compound cerate of the N. F. Jalap is said to contain 8 per cent. of resin, the amount should be given as 7 per cent. The doses as given in the work vary considerably from those of the pharmacopœia. Under the head of reflex emetics, the dose of copper sulphate is stated as thirty grains, the pharmacopœia gives it as four grains, that of tartar emetic as two grains, the official dose is  $\frac{1}{2}$  g.; we have same unpleasant remembrances of the effects of a one-grain dose of tartar emetic. The dose of sparteine sulphate is given as one grain, which is probably nearer correct than the dose given in the Pharmacopœia. The dose of all the mydriatic alkaloids (as atropine) and their salts is stated as the  $\frac{1}{150}$  grain, no variation between them being given.

Apomorphine hydrochloride is cited as being the only central

(systemic) emetic, other authorities include tartar emetic, senega and squill.

Part III is devoted to Prescription Writing, which the author states "is the dread of the young medical practitioner." This part, while brief, is quite practical, and may be of considerable value in starting the young practitioner aright, but what he should have to make him an expert in the art of prescription writing is a more extensive practice while in college. Much of the fourth year in college could be devoted, directly or indirectly, to this work, and then the young physician would be able to use his knowledge of *materia medica* intelligently and practically. In conclusion, we would state that we have examined the book with much interest, and shall have pleasure and profit in consulting its pages in the future; it is well worthy of being added to every physician's library.

C. B. LOWE, M.D.

## PHILADELPHIA COLLEGE OF PHARMACY.

### MINUTES OF THE QUARTERLY MEETING.

The quarterly meeting of the Philadelphia College of Pharmacy was held December 29th, 1913, at 4 P.M., in the Library. The President, Howard B. French, in the Chair. Sixteen members present. The minutes of the semi-annual meeting held September 29th were read and approved. The minutes of the Board of Trustees, for the meetings held September 2-16, October 7, and November 5, were read by the Registrar, J. S. Beetem, and approved.

Acknowledgments of having received notice of their election to Honorary Membership were received from Doctors Carl L. Alsberg and A. L. Winton.

The President reappointed the following as the Committee on Legislation: Warren H. Poley, Joseph P. Remington, Theodore Campbell, William E. Lee, William L. Cliffe, Richard H. Lackey.

C. A. WEIDEMANN, M.D.,  
*Recording Secretary.*

### ABSTRACTS FROM THE MINUTES OF THE BOARD OF TRUSTEES.

September 16th: Thirteen members present. The Committee on Property reported that the Library ceiling had been repaired, woodwork cleaned and varnished, new carpet (cork) put down,

and new chairs purchased. Also that the woodwork of the lower front of the College had been painted, that changes had been made in the lower Microscopical Laboratory, and that the Gymnasium had been put in first class condition.

The Finance Committee approved the recommendation that Prof. Moerk engage the services of two student assistants and Prof. Kraemer one student assistant for the College term.

The Committee on Appropriations approved the estimated amounts that would be required by the several committees and departments authorized to make expenditures.

The Committee on Scholarships.—The Chair reported that owing to the absence of the Dean in Europe, it was necessary to act on the applications presented at the October meeting of the Board and suggested that the Assistant Dean be placed on the Scholarship Committee in the interim. It was so ordered.

The Joint Committee on Instruction and Examination made a report relative to students taking the course in Bacteriology, which was adopted.

The Committee on Examinations reported that John L. Bush, Harry C. Cowles, and Paul A. Kind, having complied with all the requirements, were recommended to receive the Certificate of Proficiency in Chemistry; and that Roy L. Clark having complied with all the requirements was recommended to receive the Certificate of Proficiency in Food and Drug Analysis. These recommendations were approved.

The Committee on Announcement reported the regular issuance of the Bulletin.

A letter was read from the Secretary of the State Pharmaceutical Board relative to the fact that the highest ratings of those who had taken the June examinations had been bestowed upon two graduates of the Philadelphia College of Pharmacy.

Mr. French referred to the honor conferred upon Dr. F. B. Power, a graduate of the College, who had been awarded the Hanbury Gold Medal, and he suggested that a letter of congratulation be sent Dr. Power. This met with hearty approval and the suggestion was adopted.

An application for active membership was received and referred to the Committee on Membership.

The Treasurer's Annual Report was received, and referred to the Committee on Accounts and Audit.

October 7th: Thirteen members present. A communication was received from the Recording Secretary of the College reporting the election of E. M. Boring, Charles Leedom, and Theodore Campbell to membership in the Board of Trustees for the ensuing three years.

The Committee on Property reported that the back hall and stairway had been painted and put in good condition.

The Committee on Library reported that up to this time 5246 books had been classified, accessioned and shelf-listed.

Donations of books had been received from H. G. Kalmbach, Mrs. Wm. McIntyre, Professor C. B. Lowe, Professor Henry Kraemer and the Surgeon's General Office. A number of books had been purchased. Fifty-two persons had used the Library.

The Committee on Instruction reported that several students had removed conditions, and that several others still had conditions to be removed, and suggested rules to govern such cases in the future; also that Prof. Kraemer had selected Anton Hogstad, a third year student, as an assistant.

The Chairman stated that Professor Roddy had requested Messrs. Mulford & Company and Parke, Davis & Company to present samples of Bacteriological products to his laboratory, with which request they had complied and new products would accordingly be added. The thanks of the Board was conveyed to the donors.

The Committee on Scholarships reported the names of twelve persons to whom scholarships had been awarded.

Mr. Shoemaker read a communication from Prof. Kraemer to the Registrar relative to the fund started by the classes ending in 4 and 9, to the effect that the fund be placed in the hands of the Treasurer. The Treasurer suggested that the fund be one representing all graduates. Prof. Kraemer was requested to outline the plan undertaken by the classes and to submit such outlined plan at the next meeting of the Board.

An application for Associate Membership was received and referred to the Committee on Membership.

The Committee on Membership reported favorably on the application of George L. Sontag, of Neillsville, Wisconsin, Class of 1890. A ballot was taken and he was unanimously elected.

November 5th: Thirteen members present. Committee on Library reported an additional number of books accessioned, classified and shelf-listed and that a gift had been received from G. Mason Thompson. A number of books had been purchased. One hundred and forty-six persons had used the Library.

Committee on Instruction reported that the Sub-Committee on Special Lectures had secured outside talent to deliver nine special lectures during the College term. A wide range of subjects having been selected. Several joint meetings of the Committees on Instruction and Examinations were held to formulate some system of grading or evaluation to be attached to the results of the examinations in the various branches of the College—such system that differentiates between the Major\* and Minor branches. After earnest consideration, a plan has been proposed by which each subject of instruction will be given a rating corresponding with its importance. This plan will be put in force for the present year in order that its adaptability to the conditions now existing may be tested.

The Secretary announced that he had received letters from the recipients of scholarships expressing their appreciation.

The Chairman read a letter from Dr. F. B. Power expressing his appreciation of the good wishes and congratulations extended him by the College. The correspondence was directed to be published in the *AMERICAN JOURNAL OF PHARMACY*.

PHILADELPHIA COLLEGE OF PHARMACY.

September Twenty-third, 1913.

DR. FREDERICK B. POWER,

Snow Hill, London, E. C., England.

Dear Doctor:

The news that the Committee on Hanbury Medal of the Pharmaceutical Society of Great Britain had awarded you this year this coveted medal, has been received by the members of the Philadelphia College of Pharmacy with mingled feelings of pleasure and pride. It is now nearly forty years since your first scientific papers were published in our *JOURNAL* and we appreciate that with the harvest of material that is yours, you still remember us. It is but natural on an occasion of this kind, being probably the proudest in your life, that we in offering you our felicitations and congratulations should remind you that the successive steps in your career since graduating from our College and working in its faculty, have been followed by us with increasing interest as year by year has passed. Rarely does it fall to the lot of any one man to accomplish so much, and it is even more unusual for him to receive while yet in his prime, the recognition he deserves for the days and nights of unremitting



toil with which he has applied himself to his chosen task. We trust that you may be spared many years to continue your studies, and it is our earnest desire that the harvest may satisfy your proudest hopes and highest expectations. We wish you health that you may work easily as well as effectively and enjoy the fruits of your labors.

Very truly,

HOWARD B. FRENCH,  
*President.*

THE WELLCOME CHEMICAL RESEARCH LABORATORIES,  
FREDERICK B. POWER, PH.D., LL.D., DIRECTOR.

6, King Street, Snow Hill, London, E. C.

13 October, 1913.

HOWARD B. FRENCH, ESQ.,

President, Philadelphia College of Pharmacy,  
Philadelphia, Pa.

Dear Mr. French:

It has given me exceptional pleasure to receive your very kind letter of the 24th ultimo, and I desire to assure you of my deep appreciation of the cordial sentiments and good wishes therein expressed.

The significance of the honor attending the award of the Hanbury Gold Medal has been greatly enhanced to me by the feeling that its bestowal has also afforded gratification and pleasure to so many of my esteemed friends across the sea. The occasion of its presentation on October 1st was a memorable one, and it was a great delight to me, as indeed to the entire assembly, that Professor Remington could be present and participate in the proceedings. His remarks in seconding a vote of thanks, proposed by Sir William Tilden, F.R.S., for my address, were most felicitous, and it was altogether a grand and happy day.

I have been deeply touched by the expressions of interest manifested in my career by the Philadelphia College, which has indeed been to me a "kindly mother." I am grateful for the stimulus to scientific study which was first received as a student within its walls, and appreciate very highly the honors it has in later years conferred upon me.

In heartily reciprocating your good wishes for health and happiness, believe me to be,

Sincerely yours,

FREDERICK B. POWER.

The Committee on Membership reported favorably on the application of Otto Raubenheimer, of Brooklyn, N. Y., as an Associate Member. A ballot was taken and he was unanimously elected.

### PHARMACEUTICAL MEETINGS.

The second Pharmaceutical meeting was held on Friday afternoon, November 14, Mr. Edward M. Boring presiding.

Prof. Charles H. LaWall presented a paper on "Detection of Chicory in Decoctions of Chicory and Coffee" prepared in conjunction with Mr. Leroy Forman.

Mr. Boring then exhibited two specimens of Elixir of Iron, Quinine and Strychnine, made six months apart, their fine appearance being due to neutralization after the addition of the iron phosphate.

Prof. Remington gave a delightful talk on "Some Pharmaceutical Celebrities I Have Met," in connection with which he showed a large number of slides including portraits and views in laboratories abroad and in manufacturing houses.

### OBITUARY.

EVAN TYSON ELLIS was born in Philadelphia on August 10, 1826 and died in the same city on October 11, 1913. He was the oldest alumnus and member of the Philadelphia College of Pharmacy, the last surviving charter member of the Philadelphia Photographic Society, and for many years a prominent figure in the wholesale drug circles of Philadelphia.

Mr. Ellis came of sturdy Quaker stock, his father, Charles Ellis, being a well known Orthodox Quaker, a leading wholesale druggist and an official, in various capacities, of the Philadelphia College of Pharmacy for more than forty years. He received his education at Haverford College from which he was graduated with the class of 1844 and was one of the oldest members of the Haverford College Alumni Association. He then studied pharmacy, attended the courses of instruction at the Philadelphia College of Pharmacy, graduating with the class of 1847. The subject of his thesis was "Extract of Valerian."

After he was graduated, Mr. Ellis went into partnership with his father, Charles Ellis, in Philadelphia, and together they built up a large wholesale drug business, under the name of Charles Ellis, Son and Co. During the Civil War he served in the Hospital Department of the U. S. Army.

J. W. ENGLAND.

# THE AMERICAN JOURNAL OF PHARMACY

MARCH, 1914

## DISTRIBUTION OF ALKALOIDS IN THE BELLADONNA PLANT.\*

BY A. F. SIEVERS, Chemical Biologist,

Office of Drug Plant Investigations; Bureau of Plant Industry.

In connection with an investigation of the individual variation of the alkaloidal content of belladonna plants, it was desirable to determine the relative distribution of the alkaloids in the plant. In this article are presented the results of a complete, detailed examination of a number of such individual plants. The conclusions that may be drawn from these results are interesting in that they indicate a number of facts concerning the relative therapeutic value of various parts of the plant which may be of economic significance. Furthermore, a definite knowledge of such a distribution may eventually add to our information concerning the rôle of the alkaloids in the physiological processes of the plant.

In determining the alkaloids it was frequently necessary to assay very small samples. The method employed was that of the U. S. Pharmacopœia with some modifications of the technique to make the process applicable to small samples. These modifications have been described in some previous articles.<sup>1</sup> Analyses were made of first and third year plants.

### THIRD-YEAR PLANTS.

The analyses of the third-year plants were made in June, when they were in full bloom. Owing to the fact that most of these were reserved for other work, only four individual plants could be

\* Published by permission of the Secretary of Agriculture.

<sup>1</sup> *Merck's Report*, August, 1910, p. 215; *Journal of the American Pharmaceutical Assn.*, March, 1912, p. 199.

secured for the experiment, but these four were typical of the entire plot.

The green or aerial portion of each plant was separated into the following parts: (1) Flowers, (2) flowering tops, (3) small and large leaves, and (4) small and large stems. All the parts were immediately weighed so that the percentage of moisture could be determined. The flowers included only the open flowers. The flowering tops consisted of the tops of the branches, including about three or four inches of the young stems and the small and young leaves and flower buds. The small leaves were mostly of the younger growth, located largely near the upper part of the plant; a few, however, growing at the juncture of the old leaves and the stems. The large leaves were picked close to the stem, and the petioles at the base of the leaves were removed and kept separate. The large stems were separated from the small ones, the latter including those above the point where the large stem forks. The small stems as a rule were quite small and tender, averaging about a quarter of an inch in diameter. The large stems were split, the thin bark peeled off, and the pith, which constitutes the bulk of the interior of the stem, was scraped out. Each part was weighed separately.

The roots were carefully dug out and thoroughly washed to remove all dirt. The small roots, which consisted mainly of the young slender ends of the tap roots and secondary fibrous roots, were then separated from the large ones. The large roots, or thick tap roots, were separated into two parts, the wood and the bark.

After being thoroughly air-dried, all parts of the plants were dried to constant weight in a hot-air oven at a maximum temperature of 60 degrees C. The alkaloids were determined by the method described, and the results of the analysis of each of the four plants are shown in Table I, which is summarized at the close, in order to compare the percentages of alkaloids in the several parts of the individual plants.

#### FIRST-YEAR PLANTS.

There were six of the first-year plants, and these were analyzed in September, when the flowering was over and all but a few of the berries were ripe. The aerial portion of each plant was separated into the following parts: (1) Small and large leaves, (2) young sprouts, (3) fruit, (4) small and large stems. The fruits or berries were picked with the stem and calyx attached, the latter being after-

TABLE I.  
*Analyses of Four Typical Third-year Belladonna Plants.*

Plant and part	Weight (grams)		Moist- ure per cent.	Per cent. of entire plant	Alkaloids		
	Green	Dry			Grams	Per cent.	Percentage of quantity of alkalo- ids in the plant
Plant No. 1.							
Flowers.....	34.15	5.75	83.17	2.14	0.0255	0.445	2.27
Flowering tops.....	194.20	31.94	83.57	11.86	.2753	.862	24.42
Leaves:							
Small.....	40.36	7.55	82.68	2.81	.0512	.679	4.54
Large:							
Without petioles.	187.44	31.04	83.42	11.56	.1173	.378	10.40
Petioles.....	28.94	2.89	90.00	1.07	.0110	.381	.97
Entire large leaves.....	216.38	33.93	84.30	12.60	.1283	.378	11.37
Total.....	256.74	41.48	83.70	15.70	.1795	.432	15.90
Stems:							
Small.....	161.65	20.33	87.40	7.55	.0896	.441	7.93
Large:							
Pith.....	141.80	10.00	92.95	3.71	.0337	.337	2.98
Bark.....	95.20	10.76	87.93	3.99	.0131	.128	1.16
Wood.....	113.00	27.81	75.45	10.33	.0292	.105	2.59
Entire large stems.....	350.00	48.57	86.10	18.04	.0760	.156	6.73
Total.....	511.65	68.90	86.58	25.59	.1656	.237	14.66
Roots:							
Small.....	85.95	13.81	83.92	5.13	.0701	.508	6.22
Large:							
Wood.....	473.30	64.35	86.42	23.90	.2786	.433	24.72
Bark.....	271.70	42.95	84.20	15.95	.1331	.310	11.81
Entire large roots.....	750.00	107.30	85.60	39.88	.4117	.383	36.53
Total.....	835.95	121.21	85.40	45.01	.4818	.398	42.75
Entire plant.....	1,832.69	269.28	85.31	.....	1.1277	.418	100.

TABLE I.—Continued.  
Analyses of Four Typical Third-year Belladonna Plants.

Plant and part	Weight (grams)		Moisture per cent.	Per cent. of entire plant	Alkaloids		
	Green	Dry			Grams	Per cent.	Percentage of quantity of alkaloids in the plant
Plant No. 2.							
Flowers.....	26.67	4.55	82.95	2.04	.0126	.277	1.21
Flowering tops.....	111.55	16.63	85.08	7.50	.1280	.770	12.33
Leaves:							
Small.....	21.00	2.95	86.00	1.32	.0181	.613	1.72
Large:							
Without petioles.	183.00	27.23	85.14	12.20	.1555	.571	14.96
Petioles.....	21.65	2.32	89.30	1.04	.0194	.839	1.87
Entire large leaves.....	214.65	29.55	86.10	13.24	.1749	.592	16.85
Total.....	235.65	32.50	86.08	14.64	.1930	.597	18.57
Stems:							
Small.....	141.70	18.48	86.93	8.28	.1417	.767	13.63
Large:							
Pith.....	120.90	9.34	92.27	4.18	.0347	.372	3.34
Bark.....	82.30	9.50	88.45	4.17	.0145	.153	1.345
Wood.....	93.00	25.07	73.00	11.23	.0326	.130	3.14
Entire large stems.....	296.20	43.91	85.20	19.67	.0818	.186	7.88
Total.....	437.90	62.39	85.80	27.95	.2235	.358	21.51
Roots:							
Small.....	105.50	16.47	84.40	7.38	.0974	.592	9.36
Large:							
Wood.....	364.30	53.71	85.32	24.07	.2572	.479	24.75
Bark.....	266.70	36.93	86.07	16.59	.1274	.345	12.27
Entire large roots.....	630.00	90.64	85.61	40.61	.3846	.424	37.02
Total.....	735.50	107.11	85.44	52.52	.4820	.450	46.38
Entire plant.....	1,538.27	223.18	85.49	.....	1.0391	.466	.....

TABLE I.—*Continued.*  
*Analyses of Four Typical Third-year Belladonna Plants.*

Plant and part	Weight (grams)		Moisture per cent.	Per cent. of entire plant	Alkaloids		
	Green	Dry			Grams	Per cent.	Percentage of quantity of alkaloids in the plant
Plant No. 3.							
Flowers.....	29.75	5.26	82.30	2.03	.0191	.366	1.58
Flowering tops.....	104.00	16.29	84.32	6.29	.1379	.847	11.38
Leaves:							
Small.....	28.00	4.57	83.70	1.77	.0305	.669	2.51
Large:							
Without petioles.	186.83	28.36	84.88	10.95	.1273	.449	10.50
Petioles.....	18.67	1.69	90.99	.65	.0059	.354	.49
Entire large leaves.....	205.50	30.05	85.40	11.60	.1332	.443	10.99
Total.....	233.50	34.62	85.10	13.29	.1637	.472	13.50
Stems:							
Small.....	125.80	17.49	86.08	6.75	.0892	.510	7.36
Large:							
Pith.....	119.30	7.24	93.49	2.80	.0222	.307	1.83
Bark.....	84.60	7.98	90.35	3.08	.0113	.142	.93
Wood.....	98.50	26.86	72.70	10.37	.0306	.114	2.53
Entire large stems.....	302.40	42.08	86.13	16.24	.0641	.152	5.29
Total.....	428.20	59.57	86.10	22.99	.1533	.257	12.65
Roots:							
Small.....	212.80	36.33	82.97	14.03	.2365	.651	19.51
Large:							
Wood.....	449.90	70.54	84.30	27.23	.3900	.553	32.19
Bark.....	216.10	36.40	83.20	14.05	.1114	.306	9.19
Entire large roots.....	666.00	106.94	83.93	41.29	.5014	.469	41.38
Total.....	878.80	143.27	83.70	55.31	.7379	.515	60.89
Entire plant.....	1,674.25	259.01	84.53	.....	1.2119	.468	.....

TABLE I.—Continued.  
Analyses of Four Typical Third-year Belladonna Plants.

Plant and part	Weight (grams)		Moist- ure per cent.	Per cent. of entire plant	Alkaloids		
	Green	Dry			Grams	Per cent.	Percentage of quantity of alkalo- ids in the plant
Plant No. 4							
Flowers.....	41.60	8.00	80.60	2.83	.0361	.452	3.00
Flowering tops.....	91.00	16.37	82.00	5.79	.1607	.982	13.36
Leaves:							
Small.....	28.60	5.00	81.40	1.77	.0378	.757	3.14
Large:							
Without petioles..	185.50	30.48	83.60	10.79	.1026	.337	8.53
Petioles.....	18.60	1.62	91.30	.57	.0081	.502	.68
Entire large leaves.....	204.10	32.10	84.24	11.36	.1107	.345	9.21
Total.....	230.90	37.10	83.75	13.13	.1485	.400	12.35
Stems:							
Small.....	195.60	22.50	88.50	7.96	.1597	.710	13.28
Large:							
Pith.....	140.20	10.37	92.60	3.67	.0431	.416	3.59
Bark.....	118.00	12.31	89.58	4.63	.0136	.111	1.13
Wood.....	138.30	38.29	73.30	13.55	.0486	.127	4.03
Entire large stems.....	396.50	60.97	84.65	21.58	.1053	.173	8.75
Total.....	592.10	83.47	85.95	29.54	.2650	.318	22.03
Roots:							
Small.....	196.20	35.65	81.80	12.62	.1750	.491	14.55
Large:							
Wood.....	415.30	63.62	84.75	22.52	.3047	.479	25.33
Bark.....	229.30	38.34	83.30	13.57	.1127	.294	9.38
Entire large roots.....	644.60	101.96	84.20	36.08	.4174	.409	34.71
Total.....	840.80	137.61	83.61	48.70	.5924	.430	49.26
Entire plant.....	1,796.40	282.55	84.27	.....	1.2027	.425	.....



TABLE II.  
*Comparison of Percentage of Alkaloids in Different Parts of Plants.*

Part of plant	Alkaloids (per cent.)					Fraction of average total alkaloids in 4 plants
	Plant No. 1	Plant No. 2	Plant No. 3	Plant No. 4	Average of 4 plants	
Flowers.....	0.445	0.277	0.366	0.452	0.385	2.03
Flowering tops.....	.862	.770	.847	.982	.865	15.33
Leaves:						
Small.....	.679	.613	.669	.757	.679	3.00
Large:						
Without petioles.....	.378	.671	.449	.337	.434	10.98
Petioles.....	.381	.839	.354	.502	.769	.93
Entire large leaves.....	.378	.592	.443	.345	.439	11.94
Total.....	.432	.597	.472	.400	.475	14.95
Stems:						
Small.....	.441	.767	.510	.710	.607	10.48
Large:						
Pith.....	.337	.372	.307	.416	.358	2.97
Bark.....	.128	.153	.142	.111	.134	1.17
Wood.....	.105	.130	.114	.127	.119	3.13
Entire large stems.....	.156	.186	.152	.173	.167	7.27
Total.....	.237	.358	.257	.318	.292	17.62
Roots:						
Small.....	.508	.592	.651	.491	.561	12.63
Large:						
Wood.....	.433	.479	.553	.479	.486	26.86
Bark.....	.310	.345	.306	.294	.314	10.58
Entire large roots.....	.383	.424	.469	.409	.421	37.44
Total.....	.398	.450	.515	.430	.448	50.07
Entire plant.....	.418	.466	.468	.425	.444	.....

ward detached and kept separate. The berries were allowed to dry slowly in the air until the seeds and husks could be separated. The young sprouts, which were found mainly along the lower portions of the large stems, were from 2 to 4 inches long and consisted of tender growth of stem and leaves. Since these were first-year plants all the stems were rather small and none were large enough to be

TABLE III.  
*Analyses of Six Typical First-year Belladonna Plants.*

Plant and part	Weight (grams)			Per cent. of entire plant	Alkaloids		
	Green	Dry	Moisture per cent.		Grams	Per cent.	Percentage of total quantity in the plant
Plant No. 1							
Leaves.....	134.00	27.56	79.40	12.23	.1463	.531	21.67
Small.....	78.35	15.94	79.70	7.07	.0906	.569	13.42
Large.....	55.65	11.62	79.10	5.16	.0557	.479	8.25
Young sprouts.....	58.20	8.50	85.50	3.77	.0680	.799	10.07
Fruit.....	350.40	67.35	80.00	29.90	.1816	.269	26.90
Calyx.....	72.65	9.95	86.40	4.42	.0084	.085	1.24
Berries.....	277.75	57.40	79.40	25.50	.1732	.302	25.66
Seeds.....	.....	44.59	.....	19.86	.1536	.344	22.75
Husks.....	.....	12.81	.....	5.64	.0196	.153	2.91
Stems.....	352.80	76.68	78.40	34.05	.0752	.098	11.14
Small.....	181.30	40.72	77.40	18.20	.0493	.121	7.30
Large.....	171.50	35.96	79.00	15.93	.0259	.072	3.84
Roots.....	215.80	47.17	78.00	20.94	.2040	.432	30.22
Entire plant.....	1,111.20	225.26	79.70	.....	.6751	.299	.....
Plant No. 2							
Leaves.....	83.40	18.38	77.9	10.05	.1137	.619	18.03
Small.....	41.65	9.09	78.3	4.97	.0594	.654	9.42
Large.....	41.75	9.29	77.6	5.08	.0543	.586	8.61
Young sprouts.....	59.50	6.59	83.2	3.60	.0629	.953	9.98
Fruit.....	245.70	54.20	78.5	29.78	.1960	.361	31.08
Calyx.....	60.55	8.32	79.8	4.58	.0126	.152	1.49
Berries.....	185.15	45.88	75.3	25.20	.1834	.399	29.09
Seeds.....	.....	33.76	.....	18.55	.1618	.479	25.65
Husks.....	.....	12.12	.....	6.65	.0216	.178	3.43
Stems.....	361.15	66.63	81.3	36.50	.0788	.118	12.49
Small.....	198.00	35.79	82.1	19.60	.0566	.158	8.97
Large.....	163.15	30.84	81.0	16.90	.0222	.072	3.52
Roots.....	167.90	36.70	78.1	20.07	.1793	.488	28.42
Entire plant.....	897.65	182.5	79.7	.....	.6307	.346	.....

TABLE III.—*Continued.*  
*Analyses of Six Typical First-year Belladonna Plants.*

Plant and part	Weight (grams)		Moisture per cent.	Per cent. of entire plant	Alkaloids		
	Green	Dry			Grams	Per cent.	Percentage of total quantity in the plant
Plant No. 3							
Leaves.....	107.57	25.44	76.40	11.28	.1305	.514	20.06
Small.....	70.40	16.56	76.40	7.33	.0907	.548	13.94
Large.....	37.17	8.88	76.00	3.95	.0398	.448	6.12
Young sprouts.....	46.95	8.04	82.90	3.56	.0708	.877	10.87
Fruit.....	337.40	66.83	80.10	29.63	.2014	.302	30.93
Calyx.....	77.45	10.72	86.00	4.73	.0091	.085	1.39
Berries.....	259.95	56.11	78.30	24.90	.1923	.343	29.54
Seeds.....	.....	44.25	.....	19.64	.1733	.391	26.61
Husks.....	.....	11.86	.....	5.26	.0190	.160	2.92
Stems.....	363.50	77.03	79.00	34.15	.0564	.073	8.66
Small.....	154.10	31.93	78.00	14.15	.0298	.093	4.58
Large.....	209.40	45.10	78.50	20.00	.0266	.059	4.08
Roots.....	197.15	48.23	75.50	21.38	.1920	.397	29.48
Entire plant.....	1,052.57	225.57	78.60	.....	.6511	.288	.....
Plant No. 4							
Leaves.....	142.30	27.59	80.70	10.45	.2038	.736	20.37
Small.....	68.65	13.13	81.00	4.95	.0918	.698	9.17
Large.....	73.65	14.46	80.40	5.50	.1120	.772	11.20
Young sprouts.....	51.92	8.21	84.20	3.12	.0849	1.032	8.49
Fruit.....	398.80	75.34	81.05	28.56	.2810	.373	28.09
Calyx.....	109.45	13.90	87.10	5.28	.0294	.211	2.94
Berries.....	289.35	61.44	78.80	23.28	.2516	.409	25.15
Seeds.....	.....	49.20	.....	18.66	.2170	.441	21.69
Husks.....	.....	12.24	.....	4.62	.0346	.283	3.46
Stems.....	400.05	82.63	79.20	31.32	.1156	.140	11.55
Small.....	183.10	36.93	78.60	14.00	.0661	.179	6.60
Large.....	216.95	45.70	78.90	17.32	.0495	.108	4.95
Roots.....	238.35	70.00	70.90	26.55	.3150	.450	31.50
Entire plant.....	1,231.77	263.77	78.30	.....	1.0003	.379	.....

TABLE III.—*Continued.*  
*Analyses of Six Typical First-year Belladonna Plants.*

Plant and part	Weight (grams)		Moisture per cent.	Per cent. of entire plant	Alkaloids		
	Green	Dry			Grams	Per cent.	Percentage of total quantity in the plant
Plant No. 5							
Leaves.....	113.75	23.41	82.20	12.69	.2135	.913	28.67
Small.....	60.05	12.51	79.10	6.80	.1113	.890	14.94
Large.....	53.70	10.90	79.80	5.89	.1022	.938	13.73
Young sprouts.....	51.95	7.52	85.50	4.10	.0790	1.052	10.62
Fruit.....	295.60	58.72	80.08	31.99	.1957	.333	26.27
Calyx.....	75.06	9.69	86.90	5.27	.0148	.221	1.99
Berries.....	220.60	49.03	77.80	26.72	.1809	.370	24.28
Seeds.....	.....	37.80	.....	20.65	.1550	.409	20.81
Husks.....	.....	11.14	.....	6.07	.0259	.233	3.47
Stems.....	331.75	62.13	81.10	33.84	.0892	.144	11.98
Small.....	192.05	35.30	81.80	19.22	.0626	.177	8.41
Large.....	139.70	26.83	80.90	14.62	.0266	.099	3.57
Roots.....	126.50	31.90	73.90	17.38	.1674	.524	22.46
Entire plant.....	919.55	183.68	81.98	.....	.7448	.405	.....
Plant No. 6							
Leaves.....	107.65	20.72	80.70	10.04	.1662	.803	23.65
Small.....	57.40	10.97	80.89	5.31	.0873	.794	12.42
Large.....	50.25	9.75	80.59	4.73	.0789	.808	11.23
Young sprouts.....	37.55	6.21	83.25	3.01	.0545	.876	7.75
Fruit.....	335.85	61.29	81.50	29.69	.1700	.277	24.19
Calyx.....	80.15	9.50	88.10	4.60	.0132	.139	1.88
Berries.....	255.70	51.79	79.70	25.09	.1568	.305	22.31
Seeds.....	.....	37.28	.....	18.06	.1193	.320	16.97
Husks.....	.....	14.51	.....	7.03	.0375	.259	5.38
Stems.....	380.70	70.67	81.40	34.23	.0874	.114	12.44
Small.....	244.00	43.32	82.00	21.00	.0724	.167	10.30
Large.....	136.70	27.35	79.90	13.23	.0150	.055	2.14
Roots.....	221.50	47.54	78.30	23.03	.2247	.472	31.97
Entire plant.....	1,083.25	206.43	80.94	.....	.7028	.340	.....

separated into bark, wood, and pith. The roots also were much smaller than in the older plants and were therefore not separated into large and small roots.

In assaying the seeds it was necessary first to extract the fixed oil with petroleum ether. The percentage of alkaloids, however, as given in Table III, is calculated on the basis of the whole seeds.

TABLE IV.

*Summary Showing Comparison of Percentages of Alkaloids in Different Parts of the Six Plants.*

Part of plant	Alkaloids (per cent.)							Fraction of average total alkaloids in 6 plants
	Plant No. 1	Plant No. 2	Plant No. 3	Plant No. 4	Plant No. 5	Plant No. 6	Average of all plants	
Leaves.....	0.531	0.619	0.514	0.736	0.913	0.803	0.6860	22.10
Small.....	.569	.654	.548	.698	.890	.794	.6922	12.05
Large.....	.479	.586	.448	.772	.938	.808	.6718	10.05
Young sprouts...	.799	.953	.877	1.032	1.052	.876	.9315	9.53
Fruit.....	.269	.361	.302	.373	.333	.277	.3192	27.84
Calyx.....	.085	.152	.085	.211	.221	.139	.1488	1.99
Berries.....	.302	.399	.343	.409	.370	.305	.3572	25.85
Seeds.....	.344	.479	.391	.441	.409	.320	.3973	22.25
Husks.....	.153	.178	.160	.283	.233	.259	.2110	3.60
Stems.....	.098	.118	.073	.140	.144	.114	.1145	11.41
Small.....	.121	.158	.093	.179	.177	.167	.1492	7.65
Large.....	.072	.072	.059	.108	.099	.055	.0775	3.76
Roots.....	.432	.488	.397	.450	.524	.472	.4605	29.11
Entire plant.....	.299	.346	.288	.379	.405	.340	.3430	

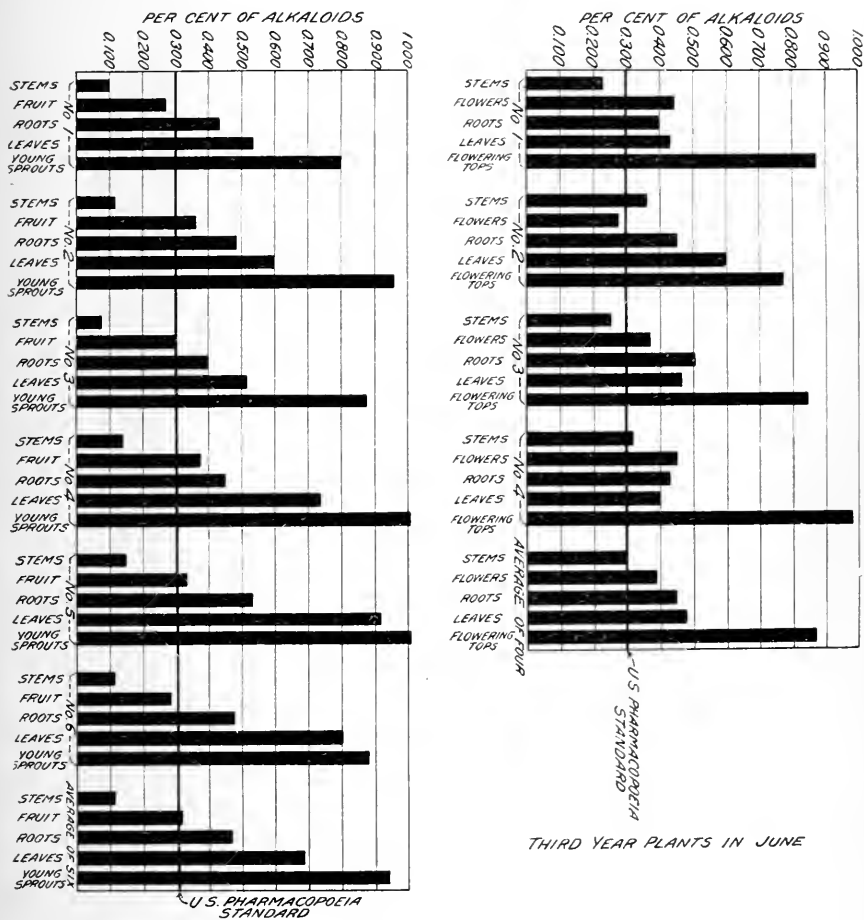
A critical review of Tables I to IV leads to the conclusion first of all that in a general way the distribution of alkaloids in the different parts of belladonna plants is largely the same in different individual plants. While it is probably unwise to draw definite conclusions from the limited number of plants here analyzed, the results are without doubt largely indicative of what would be found were analyses made of many more plants. Gerard<sup>2</sup> has found that in both wild and cultivated belladonna plants the leaves, roots, fruit,

<sup>2</sup> Gerard, A. W. Report on the alkaloidal value of cultivated and wild belladonna plants, *Yearbook of Pharmacy*, 1880-1881, pp. 482-489.

and stems rank in the order named as regards the percentage of alkaloidal content. These observations are in perfect accord with the results here given. A number of interesting facts are emphatically brought out. Of the aerial part of the plant all parts but the large woody stems contain enough alkaloids to make their utilization practicable. During the early summer, belladonna herb, including leaves, tops, and small stems, could be advantageously picked as far as medicinal strength is concerned if the herb rather than leaves were official. The flowering tops in the third-year plants easily rank first as containing the greatest percentage of alkaloids. In all the first-year plants, the young sprouts are found to contain the greatest quantity of alkaloids, two of the six containing more than 1 per cent. Attention has been directed to the fact that the flowering tops and the young sprouts represent the youngest and tenderest growth in the third-year and in the first-year plants, respectively. Since in the plants analyzed the greatest concentration of alkaloids is found in these parts, the logical conclusion is that the greatest concentration of alkaloids is to be found in the youngest parts of the plants. A further study of the tables will emphasize this fact still more. In seven of the ten plants the small leaves are considerably richer in alkaloids than the large leaves, the average for the small leaves being 0.687 per cent. and for the large ones 0.578 per cent. The small leaves usually appear on the plants later than the large ones. In the case of the third-year plants, which were analyzed in June, the small leaves were found mostly near the tops of the branches, indicating that they represented younger growth than the large leaves. Later in the season there is always a preponderance of small leaves, very little growth of large leaves taking place after the flowering period is over. Hence, in all the plants under consideration, the small leaves constitute in a general way younger growth than the large ones. The higher percentage of alkaloids in the former is, therefore, parallel to the condition that exists in the flowering tops and young shoots. Again it is seen that the same is true of the stems. The average per cent. of alkaloids in the small stems is 0.332, and in the large stems 0.113. The difference is especially marked in the third-year plants. Here again those stems which constitute the youngest growth are richest in alkaloids. In the four plants where the large and small roots were separated, the average alkaloidal content of the small roots was 0.561 per cent., and of the large roots 0.421 per cent. The small roots, as has been

stated, consisted mostly of the young and tender ends of the tap roots. The relationship is again evident. In the four third-year plants whose large stems and roots were separated into their various

FIG. 1.



Graphic illustration showing the distribution of the alkaloids in the various parts of the Belladonna plant.

parts, the average per cent. of alkaloids is as follows: Pith of stems, 0.0358; bark of stems, 0.134; wood of stems, 0.119; bark of roots, 0.314; wood of roots, 0.486. Figure I shows graphically the distribution of alkaloids in the plant.

It has been quite generally held that most of the alkaloids in the roots are found in the bark. The National Dispensatory states that a good root contains alkaloids in the parenchymal tissue of all parts though mostly in the bark, while in a woody root it is almost exclusively in the bark. This investigation appears to indicate that such is not always the case. In all of the four three-year old plants analyzed, the woody part of the roots was richer in alkaloids than the bark. In order to obtain further data on this question, seven four-year old plants were dug up early in the fall and the roots separated into bark and wood. Table V shows the results of the assays.

TABLE V.

*Comparison of Alkaloidal Content of the Bark and Wood of the Roots of Individual Belladonna Plant.*

Number of plant	Alkaloids (per cent.)	
	Bark	Wood
1	0.182	0.217
2	0.163	0.177
3	0.262	0.324
4	0.144	0.290
5	0.205	0.347
6	0.238	0.447
7	0.227	0.400

These results show further that the bark is not always richer in alkaloids than the woody tissue.

It has been pointed out that the small leaves were found to be almost invariably richer than the large leaves. This is a matter of some importance in that it becomes a factor in the method of picking leaves with regard to securing those of greatest medicinal value. To establish this fact more conclusively, large and small leaves were picked from the individual belladonna plants. At the same time leaves were also picked from a number of species of *Datura*. Table VI shows the relative percentage of alkaloids in the leaves.

It will be noticed that in only one instance, plant No. 2, does the sample of large leaves show a greater percentage of alkaloids than the smaller. In all the others the difference is greatly in favor of the small leaves, as is also indicated by the averages. All but one of the *Datura* species indicated the same condition, thus showing



that the relative concentration of alkaloids in large and small leaves, as found in belladonna, exists also in other members of the solanaceous family. Since the small leaves are as a rule younger than the large ones, it would seem that the greater concentration of alkaloids in the former is due to greater cell activity. It would be expected that there would be a general graduation in the concentration of alkaloids from the youngest to the oldest leaves. To determine this point two rows each containing about 75 plants were selected. From

TABLE VI.

*Comparison of Alkaloidal Content of Large and Small Leaves from Individual Plants of Atropa Belladonna and Various Species of Datura.*

Plant analyzed	Alkaloidal content of leaves (per cent.)		Plant analyzed	Alkaloidal content of leaves (per cent.)	
	Large	Small		Large	Small
<i>Atropa belladonna</i> :			<i>Datura stramonium</i> .....	0.268	0.418
Plant No. 1	0.342	0.657	<i>D. fastuosa</i> No. 29646.....	.438	.478
Plant No. 2	.743	.706	<i>D. gigantea</i> .....	.165	.179
Plant No. 3	.685	.915	<i>D. quercifolia</i> .....	.228	.368
Plant No. 4	.840	.929	<i>D. fastuosa</i> No. 29644.....	.423	.479
Plant No. 5	.864	.904	<i>D. stramonium inermis</i> ....	.221	.511
Plant No. 6	.718	.831	<i>D. tatula</i> .....	.218	.241
Plant No. 7	.537	.723	<i>D. tatula inermis</i> .....	.277	.271
Plant No. 8	.960	1.074	<i>D. leichardti</i> .....	.175	.189
Plant No. 9	.775	.924	<i>D. inermis</i> (red stem) ....	.190	.454
Plant No. 10	.570	.990	<i>D. stramonium</i> (red stem)	.176	.381
			<i>D. inermis</i> .....	.133	.475
			<i>D. metaloides</i> .....	.306	.441
Average ...	.703	.865	Average.....	.247	.378

each row 8 samples of leaves were picked, ranging from the smallest to the largest. Each sample was taken from the entire row so that leaves from all the plants were included. By this means, the factor of individual plant variation was eliminated as much as possible. The following table shows the per cent. of alkaloids in each sample.

In row No. 1 the average of the first and last four samples are 0.639 and 0.308 per cent., respectively, while in row No. 2 the averages are 0.695 and 0.402, respectively. It is evident that if too many of the larger leaves are included the sample will assay relatively low and will hardly give a fair indication of the value of the plant. There is a natural tendency to pick such leaves because they can be more

TABLE VII.

*Comparison of Alkaloidal Content of Belladonna Leaves, Varying in Size from the Smallest to the Largest, each Sample being a Collective Picking from the Entire Row.*

Row No. 1.		Row No. 2.	
Sample	Alkaloids (per cent.)	Sample	Alkaloids (per cent.)
1 (smallest)	0.621	1 (smallest)	0.598
2	0.706	2	0.700
3	0.664	3	0.669
4	0.766	4	0.804
5	0.598	5	0.605
6	0.406	6	0.523
7	0.110	7	0.324
8 (largest)	0.116	8 (largest)	0.212

rapidly picked owing to their size. It is economically out of the question to pick such leaves as constitute samples 1 and 2, while samples 3 to 6 should represent the best leaves available for all purposes, appearance as well as strength, and from both the medicinal and commercial standpoint.

## THE VOLATILE NATURE OF THE TOXIC CONSTITUENT OF POISON IVY.

BY CHARLES E. BESSEY.

There is a pretty general agreement among medical men that the active poisonous principle in Poison Ivy (*Rhus radicans* L., *Toxicodendron radicans* (L.) Kuntze) is a non-volatile oil, and that as a consequence poisoning without contact is impossible. Yet there are many assertions to the contrary by those who have been victims of this poisonous principle. I have heard persons assert that they had been poisoned when walking or driving by the Poison Ivy. I have always maintained a feeling of considerable doubt in regard to such cases, for it is obviously difficult to prove lack of contact.

However, I myself once suffered from a severe case of poisoning without contact, as I reported a few years ago in a paper entitled "A Preliminary Account of the Plants of Nebraska which are

Reputed to be Poisonous, or are Suspected of Being So," and published in the *Annual Report of the Nebraska State Board of Agriculture* for 1901. This account is so detailed that I repeat it here, as follows:

"An assistant brought into my laboratory a tin box full of plants, among which were many flowering specimens of the Poison Ivy. The day was hot, and the assistant had walked in the sun for a mile or more, in bringing in the plants. Knowing my susceptibility to Poison Ivy poisoning he warned me not to touch the tin box or its contents. I therefore told him to open the box while I looked on and selected the plants which I wished him to preserve for pressing. As the box was opened I leaned over and looked in, being very careful not to come into contact with the box or the plants. As the assistant took up plant after plant I pointed to others and asked him in regard to the stations where he secured them. I was very careful, as I had been very severely poisoned many times before, and did not wish to have another experience of the discomfort. Yet in a day or two I found myself suffering with the usual inflammation, only the surfaces affected were those only which had been directly exposed when I leaned over the box of plants. My face was inflamed all over, except where my beard, mustache, eyebrows, and nose made projecting protections. Above these there were small areas entirely free from inflammation. The under side of my eyebrows (the 'overhang') was thoroughly poisoned, and so was the inside of my nose (the nostrils). My right hand was severely poisoned, but here again the distribution of the inflammation was peculiar, being confined to the parts which were *directed downward* as I pointed at the various specimens in the box. Thus the proximal and middle joints of the second, third and fourth fingers, and the under side of the wrist of that hand were badly affected, while the upper side of the hand was not poisoned at all. My left hand was not poisoned, and I account for this by the fact that it was kept back and not used in indicating plants to be examined by the assistant."

I do not see how any one can escape from the conclusion that that which poisoned me so severely and so peculiarly was volatile enough to be carried up (apparently in straight lines) in the warm air which escaped from the tin collecting box (vasculum) when opened in my study. In this case there was no contact on my part with the Poison Ivy, nor with any other plants in the vasculum. I

had been poisoned too often to be careless when warned by my assistant. I am not denying the truth of Dr. Pfaff's conclusion that there is a non-volatile poisonous oil in the Poison Ivy. I am forced to conclude that there is a volatile poison, also, in this plant.

THE UNIVERSITY OF NEBRASKA.

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## APPLIED PHARMACOGNOSY.

### SOME OBSERVATIONS OF A GRADUATE.

BY J. R. RIPPETOE.

What are you going to do one year from to-day or what will you be doing? You don't know, certainly not. If it were possible for you to know, wouldn't you prepare to make that day's work a success?

Did it ever occur to you to try and imagine what kind of a world this would be if every man could begin at his deathbed and live life back to birth or in other words live his life over again with the advantages of the experience and knowledge gained in his lifetime? Old age says my days have passed but youth is full of ambition and hopes for the future.

The laws of nature give man only one life but the law of evolution gives youth all the advantages of the experience of old age. We, therefore, in our lifetime take from the present and the past varying portions of its offerings.

You are now learning the principles of Pharmacy and soon you will be as fully equipped as the learned professors and instructors in this college can teach you and as much as you are willing to learn.

The point I want to take up with you is the application of your knowledge. Some of you will, no doubt, take up manufacturing pharmacy. Those of you who will take up retail pharmacy will find my remarks equally applicable to your position.

What are the duties of a pharmacist or a pharmaceutical chemist in a pharmaceutical laboratory?

The first operation is the writing of a working formula. If an official preparation is to be made this is not difficult, but I have seen some men spend several hours in trying to calculate the quantities of each ingredient when the formula may be given to them for one fluidounce or one tablet, as the case may be, and even then

not have it correct. A formula may state the grains or minims in each fluidounce and for practical purposes it must be calculated to the proper quantities to make 100 liters.

As many liquids are bought and sold by weight and it is also more practical to handle them by weight the minims must be converted into grammes and kilos. The specific gravity of the liquids, therefore must also be considered. Calculating many liquids to weight is absolutely necessary for figuring costs.

The quantity to be made is primarily governed by the demand but there is to be considered among other things cost of raw material. This is particularly to be considered with crude drugs which at times offer about as much opportunity for speculation as stocks in Wall Street. With such drugs as ergot, jalap, ipecac, hydrastis and opium varying in price from 50 cents to \$10.00 per pound and the price fluctuating with the season or crop it is necessary to keep an eye on the market and your stock and sales.

The buying of crude material and selling of the finished products are of course taken care of by separate departments, but the manufacturing comes in between and requires some knowledge of the buying and selling. The buying and selling departments offer good inducements to college trained men, the selling in particular to men who are more inclined to the commercial side rather than the scientific side of pharmacy.

If a fluidextract or some drug preparation is to be made and there is no stock of crude drug on hand the purchase of drug is taken up with the buying department. The buying department asks for quotations and samples of the drug offered, especially if the drug is one that has some official standard. The samples are carefully examined for freedom from foreign drugs and assayed for alkaloidal or extractive content.

The analytical reports are compared and the price also taken into consideration for selecting the lot of drug to be purchased. With assayed drugs for example the price may not vary very much but the alkaloidal content may vary as much as 100 per cent.

Since most drug preparations are made by extracting the drug with an alcoholic menstruum varying in strength from 10 to 95 per cent. absolute alcohol, and alcohol costs about \$2.50 per gallon by the barrel, means must be employed for carrying out the operations to prevent loss in handling, evaporation and final recovery from the exhausted drug.

All liquids are best handled by allowing them to flow from one vessel to another by gravity or by means of pumps to produce both pressure and vacuum as may be required.

Ofttimes it is necessary to carry out a number of experiments to determine the best combination of alcohol and water, and sometimes with glycerin or acid added, to extract the desirable constituents.

In the making of pills and tablets, excipients or the proper liquid for granulating the ingredients are to be considered. This requires a knowledge of the properties of the ingredients. In making tablets the ingredients may be granulated by adding water, alcohol, ether, chloroform, petroleum benzin, other volatile liquids or combinations of these.

Many formulas that are official in the U. S. P. or N. F. are practical for small quantities or immediate use but for large quantities and indefinite future use are not always satisfactory. The U. S. P. permits modification of the methods providing the finished products do not differ in their properties. Therefore, even in the official preparations, we have numerous problems for investigation. Elixir Iron, Quinine and Strychnine Phosphates U. S. P. is a splendid example of the manufacturers' problems and for that matter the retail druggist also. Every issue of the various drug Journals brings forth some new suggestion until it seems every one must have a different method for making it.

Elixirs or similar preparations are very popular as a means for administering most any drug and I might say whether it has merits or not. They are often very troublesome to make. Prior to the Food and Drugs Act and even now, in some few cases everything seemed to be sacrificed for elegance in appearance, color, flavor, etc., and the ingredients claimed to be present were conspicuous by their absence excepting in the very imposing gun-shot formula upon the label.

The pharmacist in filling a prescription can excuse his or the physician's unintended precipitating mixtures by putting on a "shake well" label but not so with the pharmaceutical manufacturer. Only clear non-precipitating preparations can be sent out, and there must not be any changing in color and ofttimes druggists expect them to stand storage in zero temperature and serve for a window display in a window subject to the sun's rays throughout the day.

We must, therefore, consider the solubility, stability, incom-

patibility or means for controlling any one or all of these properties of each and every ingredient in the preparation. And last but not least the color and flavor must be pleasing to the eye and taste.

It is these characteristics, the last two in particular, that have built up the pharmaceutical manufacturer's business at the expense of the druggist, and the physician's ability as a prescription writer.

You might think the manufacturer has his formulas all highly perfected and there is nothing more to be done. This is not always the case. Purer chemicals are produced, solubilities and incompatibilities may be changed or some new procedure of manipulation is learned. We therefore have before us a continual line of substances and preparations for research.

If a new or modified formula is to be made up it is always advisable to make up a small quantity, taking note of each step and carefully observing just what reactions take place. Possibly a number of combinations are indicated and about the only way to prove their value is to make up the combinations and test them out under all conditions. Each lot may be divided into portions and one of each placed in the sunlight, a hot closet, an ice box, humid atmosphere and a control under normal conditions.

When the satisfactory combination is decided upon, the manipulation and apparatus for handling large quantities is to be considered.

Means for weighing and measuring, mixing, mechanical apparatus, kettles for heating, filtering, storage, bottling or filling packages are problems always to be solved. Since the difference between raw material and finished product is labor, practical apparatus and economical manipulation stand between profit and loss.

After the preparation is finished and oftentimes during the operation various assays are made to check up the process, also for standardized preparations which are usually made overstrength and adjusted by assay. Fluidextracts, elixirs, syrups, etc., are assayed for alcohol, alkaloids, extractive, specific gravity; tablets and pills for weight and ingredients; ointments for grittiness, also powders; emulsions for efficiency of emulsification, etc.

As the majority of men seeking employment in a pharmaceutical laboratory prefer to get into the analytical department I want to say a few words about the work. I don't mean to be sarcastic or to ridicule any one, but I want to point out to you the problems by telling you how they should not be done.

I trust that every student in this audience will receive his diploma at the appointed time. We occasionally meet students who go to college for a diploma and not an education. I recall a classmate of mine who took his freshmen year in this college and did not show up again until the senior year. He stated that he had spent his junior year in another college taking a Ph.G. degree and by returning here for the senior year would receive another degree. Possibly a man with as much ability to corner the market in degrees will succeed in his own way.

Many graduates seem to think that with commencement study ends. If that is the way you feel about it you want to change your future plans at once.

I recall a former analytical assistant of mine who considered attending pharmaceutical and chemical association meetings and the reading of journals a waste of time. His work was typical of his knowledge.

Upon asking him why he ignited a tablet, which had been given him to test for morphine, he replied that he was going to test the ash for the morphine. When told he was not getting the results he should in making a preparation he stated that he had not studied it in college. If I felt that way about my work I would have to stay in college the balance of my life.

One of the most essential things in your work is several good drug journals and if interested in chemistry a journal on chemistry also. They are absolutely necessary if you want to keep abreast of the times. You may have plenty of ideas of your own to keep you busy but the other fellows have some too and unless you take advantage of the new discoveries that are being announced every day it won't be many years until you will find yourself surrounded by cobwebs of a vintage of the year you graduated.

Some men will say I haven't the time to read journals or I haven't the money. Membership in the American Pharmaceutical Association is \$5.00 a year and the best drug Journal can be had for \$1.50 per year. Two cents a day will pay for them. As to time, thirty minutes a day would more than suffice to read every line in the two publications and at the same time do a little thinking, also to see that each number is put away in some systematic manner for future reference.

I recall two men who have been my assistants by the way they did analytical work with pencil and paper rather than with the bal-



ance and burette. Why all this detail anyhow? The U. S. P. contains many tests and assays for determining the purity of the official preparations, but these men seemed to think that since the majority of samples received for testing were all right, they could make a guess at the purity, figure the results backward and get out of doing the tedious work which for them required too much patience. Quite naturally their methods were soon detected and fortunately no harm came of it outside of the laboratory. But we cannot say as much for them. They were destroying their self-respect, ambition and their opportunities for success.

These are the kind of men you are most likely to hear saying in after years, "I never had a chance."

Confidence in your ability is essential but some men are so conceited about it that they become blinded to their errors. It might be all right to have the other man believe you thoroughly capable but you should not let that feeling prejudice the analysis of your own mind and knowledge. When the other man finds you out his confidence in you will be very much weakened.

This failing may be attributed to several reasons. It is usually due to narrow-mindedness, snobbishness, false pride, all of which are due to ignorance. It indicates the failure to have grasped the primary objects in attending college, namely, to obtain a knowledge of the basic principles of the subject and the failure to continue the line of study after leaving college. Give the text-books you are using here the most prominent place in your future undertakings and add to them from time to time when some good book useful, particularly for reference, is called to your attention. These books with the Journals mentioned before are the backbone of your success. Speaking of mistakes, I recall a former assistant who was very confident of his ability and would have you believe that his knowledge was complete, he could make any kind of an analysis, he could not be in error. He said he was not in error when he obtained a result much too low in assaying a sample of ipecac but the method was faulty. He tried it again several times, always obtaining a different result which was much too low. After his last failure I picked up a beaker which he had used for evaporating the ethereal solution of the alkaloids and subsequent titration and called his attention to the resinous mass of alkaloids coating the side of the beaker which he had failed to dissolve in the volumetric acid solution. Another man required over one day to find out that a sample

labelled sodium thiosulphate was not what it was labelled, and then he spent several hours more in finding out that it was potassium nitrate.

I could tell you of many more such incidents. It is almost unbelievable that men who have been graduated by leading institutions of learning can be so helpless. The problems of the competition of life bring us to our senses and then we realize the opportunities that have been thrown away.

Coming back to my opening question, "What are you going to do one year from to-day?" If you take advantage of the opportunities before you during the year, you will be well equipped to consider with intelligence any problem that may be presented to you one year from to-day.

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## THE ASSAY OF ZINC STEARATE.

BY HANS GESELL.

In the last few years the use of Zinc Stearate as an antiseptic and astringent has been constantly increasing; it is rather difficult, however, to obtain this salt free from impurities, namely alkalis, alkali earths, chlorides, and oleates. The tests in the Pharmacopœia do not give concordant results, so there is no question of the desirability of assay methods which will be accurate, yet simply and rapidly carried out by analysts. An excess of Zinc Oxide and Zinc Oleate seem to be the most frequent admixtures.

The usual analytic method by which the stearic acid is liberated by means of hydrochloric acid and floats on the surface of the hot liquid, also holds good for any Zinc Oleate present, and if not in excess, will even congeal with the stearic acid on cooling. This difficulty can easily be overcome as follows:

Take 1 gm. of Zinc Stearate and heat with 10 c.c. of distilled water and 1 c.c. of hydrochloric acid. The Stearic and oleic acid will be liberated and float as an oily layer. Let cool and this layer will solidify. Pour off acid liquid and wash the cake several times with water. Let dry. Determine the melting point. Pure Stearic acid melts at 69°, but as the Stearic acid of the market usually contains Palmitic acid, the melting point is usually 55–56°. Therefore, the melting point of this cake should not be below 55°—a lower melting point would surely point to the presence of oleic acid.

The residue after incineration which is chiefly Zinc Oxide should be about 13 per cent. It is certain Zinc Oxide does not harm in a preparation of this nature, yet it is advisable to determine if it is really Zinc Oxide. It is best done in the following manner:

Take 5 gm. of Zinc Stearate, add 10 c.c. of  $\frac{1}{2}$  N HCl and warm gently until all the Zinc Stearate is decomposed. Then with  $\frac{1}{2}$  N NaOH (Dimethyl Orange) titrate back the hydrochloric acid not used. Subtract this from the 10 c.c. taken, multiply it by the factor of Zinc Oxide, divide by the weight of Zinc Stearate taken, this will give the amount of Zinc Oxide in the compound. The Stearic acid could also be liberated and determined here, by simply separating the two liquids (warm), rejecting the aqueous portion, using phenolphthalein as indicator and titrating with  $\frac{1}{2}$  N NaOH.

In a series of 5 experiments the following results were obtained:

Melting point	Residue after incineration	Zinc found
49—50°	19.3 per cent.	15.1 per cent.
55—56°	13.6 per cent.	10.8 per cent.
55—56°	13.8 per cent.	10.9 per cent.
54—55°	14.6 per cent.	11.2 per cent.
55—56°	18.7 per cent.	14.8 per cent.

## THE SALE OF BICHLORIDE TABLETS.<sup>1</sup>

### A DISCUSSION OF THE NEED FOR RESTRICTION OF THE SALE AND DISTRIBUTION OF BICHLORIDE OF MERCURY TABLETS.

BY MARTIN I. WILBERT,

Technical Assistant, Hygienic Laboratory, United States Public Health Service.

Some months since an alleged case of accidental poisoning by corrosive mercuric chloride, in Macon, Ga., was "featured" in practically all of the daily papers of the United States in such a way as to lead the unknowing to infer that poisoning by this substance guaranteed not alone a sure but also a painless death.

The notoriety given this case was followed by an apparently unusual number of corrosive sublimate fatalities, reported from the

<sup>1</sup> Reprint from the Public Health Reports, vol. xxviii. No. 46, Nov. 14, 1913.

various parts of the United States; and the publicity given to the harrowing details in connection with several of the cases was in turn followed by agitation for legislation on the part of some of the firm believers in the power of statute law to right all wrongs and to correct or, better, to prevent all possible abuses.

Bills designed to restrict fatalities from the accidental taking of tablets containing corrosive mercuric chloride have been introduced in several of the State legislatures. In Pennsylvania, an act prohibiting the sale of bichloride of mercury at retail except upon the prescription of a registered physician was adopted by both houses of the legislature, but vetoed by the governor for the reason that "the public is amply protected regarding this drug by the restrictions put upon the sale of other poisons. Besides, I am informed that it is a household commodity." As the agitation for special legislation to restrict or at least regulate the sale of tablets of corrosive mercuric chloride is destined to be revived by the supposedly accidental poisoning of a Brooklyn business man and to continue for some time to come, it may be of advantage to review briefly the several factors involved, the abuses really existing, the propositions that have been made to correct them, the safeguards already established, and the possible ways and means of bringing about desirable changes.

While it will generally be admitted to be impracticable to prevent suicide or violent death by law or regulation, it is nevertheless well recognized that despondent and melancholy humanity is ever ready to seize upon any suggestions that offer sure, speedy, and painless death, so that every report of death, accompanied by the details of the means and methods producing it can be counted on as an incentive for other deaths brought about in much the same way.

It is perhaps unfortunate that, for the rational study of the problem before us, no definite and satisfactory information is available as to the conditions actually existing in our own country. Our mortality statistics give only general death rates and standardized death rates, without furnishing any, even approximate, information regarding the nature of the poison used or taken in cases of reported fatalities. There is, however, available in the report of the registrar-general of births, deaths, and marriages for England and Wales, a detailed account of the nature and kind of substances used, both in suicides and in accidental deaths, and a careful study of the tables herewith presented will suffice to demonstrate the impracticability of legislating specifically for any one poison. The tables also at

least suggest the fact that there is probably little or no cause for undue excitement in regard to the possible number of deaths from the internal use of corrosive mercuric chloride and that, granting that conditions in England and this country are much the same, corrosive mercuric chloride plays but a minor part in the number of deaths due to ingested poison. This fact is further emphasized when we realize the very widespread use and, incidentally at least, abuse, of tablets of corrosive mercuric chloride and the comparatively few fatalities on record resulting from its internal administration. Even a careful search of the literature since the report of the case at Macon, Ga., shows that possibly 15, certainly not over 20, deaths have been reported from the ingestion of corrosive mercuric chloride since that time. When we remember that in the registration area

*Suicides and accidental deaths from scheduled poisons reported by the registrar-general of births, deaths, and marriages for England and Wales for the year 1911.*

Poison.	Suicides.			Accidental deaths.			Total deaths.
	Male.	Female.	Total.	Male.	Female.	Total.	
Aconite and belladonna liniment	...	1	1	..	1	1	2
Antimony (?)	...	...	...	1	..	1	1
Arsenic	4	1	5	1	2	3	8
Atropine	2	...	2	..	..	...	2
Belladonna	...	1	1	1	3	4	5
Belladonna liniment	1	...	1	...	...	...	1
Cantharides	...	...	...	..	1	1	1
Carbolic acid	32	57	89	6	4	10	99
Chloral hydrate	1	...	1	2	..	2	3
Chlorodyne	1	1	2	1	3	4	6
Chloroform	1	...	1	..	1	1	2
Cocaine and aconite	1	...	1	..	..	...	1
Cresolene	...	2	2	..	..	...	2
Hydrocyanic acid	22	2	24	3	..	3	27
Lysol	1	2	3	..	..	...	3
Mercuric chloride	3	2	5	2	..	2	7
Narcotic (kind not stated)	1	...	1	4	2	6	7
Nicotine	7	1	8	..	..	...	8
Opium (laudanum and morphine)	37	11	48	41	17	58	106
Oxalic acid	42	33	75	5	10	15	90
Paregoric	...	...	...	..	1	1	1
Potassium cyanide	33	3	36	5	..	5	41
Strychnine	7	6	13	1	3	4	17
Sulphonal	...	...	...	2	..	2	2
Vermin killer	1	1	2	..	..	...	2
Weed killer	1	...	1	..	1	1	2
White precipitate	...	1	1	..	..	...	1
Total	198	125	323	75	49	124	447

*Suicides and accidental deaths from non-scheduled substances reported by the registrar-general of births, deaths, and marriages for England and Wales for the year 1911.*

Poison.	Suicides.			Accidental deaths.			Total deaths.
	Male.	Fe-male.	Total.	Male.	Fe-male.	Total.	
Acetanilide.....	..	..	..	..	1	1	1
Acetic acid.....	1	1	2	..	..	..	2
Alcohol.....	..	..	..	2	..	2	2
Ammonia.....	1	7	8	7	7	14	22
Camphor.....	2	..	2	..	..	..	2
Camphorated oil.....	..	..	..	1	1	2	2
Caustic potash.....	..	1	1	..	..	..	1
Caustic soda.....	1	..	1	2	1	3	4
Chloride of lime.....	1	..	1	..	..	..	1
Chromic acid.....	1	..	1	..	..	..	1
Disinfectant (?).....	..	1	1	2	..	2	3
Hartshorn and oil.....	..	..	..	1	..	1	1
Hydrochloric acid.....	43	30	73	19	7	26	99
Liniment (?).....	..	2	2	1	..	1	3
Mercury (?).....	1	..	1	1	..	1	2
Methylated spirit.....	..	..	..	..	2	2	2
Nitric acid.....	1	3	4	..	..	..	4
Paraffin.....	..	1	1	..	1	1	2
Pennyroyal.....	..	..	..	..	1	1	1
Phosphorus.....	1	7	8	1	1	2	10
Potassium bichromate.....	2	2	4	..	..	..	4
Potassium binoxalate.....	1	2	3	1	..	1	4
Potassium bromide.....	..	..	..	1	..	1	1
Potassium permanganate.....	..	1	1	1	1	2	3
Saltpeter.....	..	..	..	2	..	2	2
Sulphate of copper.....	..	1	1	..	..	..	1
Sulphuric acid.....	4	1	5	3	..	3	8
Veronal.....	..	2	2	8	9	17	19
Whisky.....	..	..	..	1	..	1	1
Zinc chloride.....	..	..	..	1	..	1	1
Kind not stated.....	39	21	60	13	15	28	88
Total.....	99	83	182	68	47	115	297

of the United States upward of 5000 deaths from acute poisoning are reported annually, even these apparently large figures are suggestive as being comparable with those included in the appended tables copied from the report of the registrar-general for England and Wales.

Corrosive mercuric chloride was introduced as an antiseptic in surgical procedure more than 30 years ago, and for two decades at least was widely known by the popular names "corrosive sublimate," "bichloride," or "sublimate," and used in the form of solutions for a variety of purposes. This widespread use led to its employment

in other directions, so that at the present time the statement made by the governor of Pennsylvania that bichloride of mercury "is a household commodity" is altogether too true, particularly of the tablets—pounds, if not tons, of which are sold annually for other than medicinal purposes.

A survey of the current price lists of five of the larger manufacturers of pharmaceutical preparations in the United States, presents some rather startling information, and suggests a really valid reason why tablets of corrosive mercuric chloride may be considered to be more important factors in the health and welfare of many members of the community than is generally supposed. Perhaps the most startling discovery is the fact that not a single manufacturer of tablets of corrosive mercuric chloride markets them under a name properly indicating the nature of the materials contained therein. In the lists referred to we find, under corrosive sublimate, mercuric chloride or mercury bichloride, a cross reference to antiseptic tablets or antiseptics, and under this heading the several price lists mentioned would present the following composite table:

*A composite list of antiseptic tablets from the current price lists of five leading manufacturers.*

*Antiseptic disks.*—Compressed. Green or white. Corrosive mercuric chloride 0.5 gm. with ammonium chloride.

*Antiseptic tablets.*—Compressed. White, blue, green, red, or pink. Corrosive mercuric chloride 0.5 gm. with ammonium chloride.

*Antiseptic tablets.*—White, blue, green, or red. Corrosive mercuric chloride 0.5 gm. with sodium chloride.

*Antiseptic tablets, alkaline.*—White, or pink. Sodium borate, sodium bicarbonate, sodium salicylate, sodium benzoate, sodium chloride, oil of eucalyptus, thymol, menthol, oil of gaultheria.

*Antiseptic tablets, alkaline, effervescent.*—White or pink (?). These tablets are superior to those usually sold, which harden with age and dissolve with difficulty.

*Antiseptic tablets, alkaline, improved.*—White or pink. Formula same as alkaline antiseptic tablets with addition of hydrastine hydrochloride and sanguinarine nitrate.

*Antiseptic alkaline, improved.*—Valuable as an injection in urethritis, vaginitis, and all diseases of the urethral and vaginal passages requiring a mild antiseptic and deodorant.

*Antiseptic tablets, Bernays, small.*—White, blue, or pink. Corrosive mercuric chloride 0.125 gm. with citric acid.

*Antiseptic tablets, Bernays, large.*—White, blue, or red. Corrosive mercuric chloride 0.5 gm. with citric acid.

*Antiseptic tablets, Bernays, special large.*—White or blue. Corrosive mercuric chloride 0.45 gm. with citric acid.

*Antiseptic tablets, Clover.*—White, blue, or pink. Corrosive mercuric chloride 0.45 gm. with citric acid.

*Antiseptic tablets, cyanide.*—White or pink. Mercuric cyanide 0.5 gm. with sodium borate.

*Antiseptic tablets, detergent.*—Sodium bicarbonate, sodium borate, sodium salicylate, eucalyptol, menthol, and oil of wintergreen.

*Antiseptic tablets, detergent, improved.*—Contain in addition to the ingredients mentioned above, sanguinarine nitrate and hydrastine hydrochloride.

*Antiseptic tablets, diamond.*—White, blue, or pink. Corrosive mercuric chloride 0.5 or 0.125 gm. with citric acid.

*Antiseptic tablets, external.*—White, green, pink, or blue. Corrosive mercuric chloride 0.5 gm. with ammonium chloride.

*Antiseptic tablets, La Place.*—Corrosive mercuric chloride 0.25 gm. with tartaric acid.

*Antiseptic tablets, mercuric bichloride, Young's.*—Blue. Nine varieties.

*Antiseptic tablets, mercury cyanide.*—White or pink. Mercuric cyanide 0.5 gm. with sodium borate.

*Antiseptic tablets No. 3.*—White or pink. Mercuric cyanide 0.5 gm. with borax.

*Antiseptic tablets, St. J. Perry.*—White or pink. Mercuric cyanide 0.5 gm. with ammonium chloride.

*Antiseptic tablets No. 6.*—Very soluble. White or blue. Corrosive mercuric chloride 0.5 gm. with citric acid.

*Antiseptic tablets, potassium permanganate.*—Compressed. Five varieties.

*Antiseptic tablets, St. J. Perry.*—White or pink. Mercuric cyanide 0.5 gm. with borax.

*Antiseptic tablets, tartaric sublimate.*—Corrosive mercuric chloride 0.25 gm. with tartaric acid.

*Antiseptic tablets, Young's.*—Blue. Corrosive mercuric chloride. Nine varieties.

*Antiseptic tablets, Wilson's.*—White, green, pink, or blue. Corrosive mercuric chloride 0.5 gm. with ammonium chloride.

The tablets in this list containing corrosive mercuric chloride are marketed in 16 varying sizes, 5 different shapes, and 5 different colors. Three of the shapes are distinctive and probably proprietary in nature. Obviously the most objectionable feature is the confusion which may arise from the totally misleading name applied to tablets containing highly toxic materials.

The possible abuse arising from the use of a totally misleading name for poisonous substances is further emphasized by the statement recently made by one of the agitators for legislation to provide a distinctive shape for "antiseptic tablets." This writer says: "It is a known fact that the tablets of corrosive sublimate are very easily



procured, and are used to a very large extent as a home remedy, hence they are not looked upon as the dangerous agents that they really are in the hands of the careless and ignorant."

Among the many suggestions that have been made to compel uniformity in shape and size of tablets of corrosive mercuric chloride, we have proposals to have them triangular, coffin-shaped, kidney-shaped, and in the shape of a skull, in addition to the various forms already in use. Suggestions have also been made to enact laws to compel manufacturers to color these tablets red, green, blue, yellow, and pink; also to give them a distinctive odor, and to compel their being dispensed in a uniform and distinctively shaped bottle; all of which, if it were practicable to enforce uniformity in all States and with all manufacturers, would at best tend to elaborate on the misuse of tablets of this kind, rather than to prevent accident, or their use as a poison for suicidal purposes.

Even at the present time there is sufficient legislation, if enforced, to serve as a reasonable safeguard in connection with the sale of corrosive mercuric chloride at retail. No less than 38 States include corrosive sublimate specifically in the laws designed to restrict the sale of poisons, and in but one of the existing laws, that of Utah, are corrosive sublimate tablets exempted from registration in the poison register, otherwise uniformly required for the sale of corrosive sublimate itself. During the present year, three States, Oregon, Nevada, and California, have enacted modified poison laws and specifically enumerate tablets of corrosive sublimate as belonging in "Schedule A," drugs, the sale of which is required to be registered in a book provided for that purpose. These several States also specifically enumerate "antiseptic tablets containing corrosive sublimate," being, so far, the only States recognizing the present-day custom of labelling these very toxic preparations, "antiseptic tablets."

In addition to specific agitation for the proper labelling of all preparations containing poisonous substances, the most promising innovation is the suggestion that a type form of corrosive mercuric chloride tablet or pastille be introduced in the Pharmacopœia of the United States, with a view of providing adequate safeguards to prevent accidental poisonings. While the suggestions that have been made for this purpose are many and varied, it would appear that, in view of the rapidly growing intercourse between the different countries of the world, it might be desirable to secure international uniformity in regard to preparations of this type. It has been pro-

posed, unless specific and valid objections could be offered, to adopt for inclusion in the Pharmacopœia of the United States the description of mercuric chloride pastilles included in the German Pharmacopœia. This latter Pharmacopœia provides that pastilles of mercuric chloride consist of equal parts of corrosive mercuric chloride and sodium chloride, and requires that the pastilles be colored bright red with aniline dye, have a cylindrical shape, and be twice as long as thick. These tablets or pastilles must be wrapped individually in black paper, bearing the German equivalent of the word poison in white letters. The weight of a tablet must be stated, and the wrapped tablet is to be dispensed only in suitable glass bottles or tubes.

As an argument for including in the Pharmacopœia of the United States an official tablet of corrosive mercuric chloride, rather than enacting legislation to compel uniformity in the shape, size, color, and odor of all tablets containing corrosive mercuric chloride, it has been pointed out that inclusion in the Pharmacopœia would not in any way interfere with the legitimately established trade of manufacturers, but would tend to discourage the sale and use of such preparations and bring about the gradual popularization of the official tablet. If, in addition to this, it were practicable to induce manufacturers properly to label all of their preparations so as to indicate the presence of any highly toxic substance, and then to suggest to purchasers of tablets of this kind the need for keeping them apart or in such a way that they could not readily be mistaken for other nontoxic preparations, little or no additional legislation would be necessary, unless it were to restrict newspapers from publishing unnecessary details in regard to the nature and kind of poison used in cases of accidental or intentional poisoning.

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## PROGRESS IN PHARMACY.

A QUARTERLY REVIEW OF SOME OF THE MORE INTERESTING LITERATURE RELATING TO PHARMACY AND MATERIA MEDICA.

BY M. I. WILBERT, Washington, D. C.

An unusual amount of activity is being reflected in current pharmaceutical and drug journals. While much of this activity is more or less closely related to renewed interest in the revision of the Pharmacopœia, awakened by the publication of the first instal-

ment of Abstracts of Proposed Changes, with New Standards and Descriptions to be included in the U. S. P. IX, legislation and the prospective meetings of national and state associations are also being actively discussed in all sections of the country.

LOOKING AHEAD.—The editor of the *Bulletin of Pharmacy* suggests some reform measures for the A. Ph. A., which deserve the careful attention and the hearty co-operation of every member of that association. The proposed reforms of immediate interest concern the coming meeting of the A. Ph. A., more particularly the program of section meetings. Not the least important of the suggestions made is the proposition to have the Council meeting held in the evenings so as to eliminate the constantly increasing interference of the Council meetings with the meetings of the sections. Another proposition of considerable interest is the suggestion to restrict the scientific meetings of the Association sections to two sessions a day. The third proposition is to eliminate from the now existing sections such as do not warrant continuance and thus restrict the scientific business of the Association to simultaneous sessions of a limited number of sections for a sufficient number of days to transact all of the business in hand. If in addition to these several reforms the unnecessary interference by entertainment features could be eliminated, there is no reason why the meetings of the American Pharmaceutical Association should not be held as are the meetings of the American Medical Association, in from 3 to 4 days, allowing the additional days of the week for entertainments or for the meetings of correlated societies and associations that choose to convene at or about the same time that the American Pharmaceutical Association does. Mr. Mason truthfully says that the existing trouble with the A. Ph. A. "arises from too much energy instead of too little, and what is needed is that this energy in its manifold manifestations be harnessed up and co-ordinated in a more intelligent manner. . . . The situation at Nashville last August was one of confusion worse confounded. There were the seven regular sections of the Association, each holding two or three sessions. There was the annual meeting of the National Association of Boards of Pharmacy with four or five sessions. There was the annual meeting of the Conference of Pharmaceutical Faculties, and the joint conference of the section on Education and Legislation of the A. Ph. A. . . . With it all there was no let-up in the work from nine o'clock in the morning until one or two o'clock the next morning. Everybody was

tired out. Everybody was more or less befuddled by the multiplicity of business. . . . The A. Ph. A. has outgrown the clothes of a growing youth and now needs the equipment of the adult it has come to be. Particularly are the annual meetings in need of reform if they are successfully, intelligently and efficiently to handle the vast amount of work undertaken by the Association."—*Bull. Pharm.*, 1914, v. 28, pp. 67-70.

DRUG TRADES' CONFERENCE.—A meeting of the National Drug Trades' Conference was held at Washington, January 12 to 14, all of the several national organizations being represented. Among the resolutions adopted by the Conference were:

One asking newspapers to omit as far as possible all detail of poisons or other instruments employed in suicide and murder.

One recommending that legislation relating to methods of packing and labelling of corrosive mercuric chloride tablets and other dangerous toxic drugs be deferred, pending a report by the Committees of Revision of the Pharmacopœia and the National Formulary, and tendering such aid as the members of the conference may be in a position to give in making the revision, in order that suitable regulation with respect to these drugs may be made.

One requesting the Postmaster-General to change paragraph 5 of section 472 of the postal regulations, so as to permit the mailing as first-class matter of poisonous substances packed in metal containers, bearing the name of the sender and the word "Poison."

One requesting that the Committee of Revision of the United States Pharmacopœia consider the desirability of inserting in the forthcoming revision of the United States Pharmacopœia a section defining the word "poison."—*Drug. Circ.*, 1914, v. 58, p. 99.

POISON BOTTLES.—*Anon.* The use of a special bottle for poisons is not enforced by law in the United States, although legislation embodying the principle has more than once been attempted in various States. On what grounds the proposals have been rejected we cannot understand, for there is ample proof in the experience of our own country that the "poison bottle" is an excellent danger signal.—*Pharm. J.*, 1914, v. 92, p. 89.

RESTRICTION OF SALE OF COAL-TAR SYNTHETICS.—The Kansas City Association of Retail Druggists is conducting an energetic movement toward legislation prohibiting the sale of antipyrin, acetphenetidin, and acetanilide, except on physicians' prescriptions.—*Drug. Circ.*, 1914, v. 58, p. 103.

**DRUG STORE STRIKE.**—The advantages of efficient organization and co-operation are well emphasized in a recent number of the *Pharmazeutische Post* (December 24, 1913, v. 46, pp. 1109-1112), which publishes an illustrated description of a successful drug store strike in Argentine brought about by a proposal to increase the stamp tax on specialties and perfumery, and to impose a complicated method of control which the druggists of Argentine considered impracticable. The strike was general, every drug store in Argentine closing on a given date and the concerted action promptly resulted in the law being set aside for the time being and subsequently revised.

**USEFUL DRUGS.**—An editorial designates the recently published volume on Useful Drugs as a book with a purpose that will mark an era in American medicine and will likewise have a distinct effect upon American pharmacy. The editor criticizes the inclusion of syrup of sarsaparilla on the mistaken supposition that its use is recommended as a vehicle but concludes that even this is a minor matter and Useful Drugs has a purpose and also has a future.—*Drug. Circ.*, 1914, v. 58, p. 66.

In a book review, p. 98, the same journal adds: "Useful Drugs can therefore be described as the ideal epitome, and the pharmacist interested in his prescription department will do well to aid in the circulation of the work by distributing it among physicians of his own neighborhood."

**DIGEST OF COMMENTS ON THE PHARMACOPŒIA OF THE UNITED STATES OF AMERICA.**—A book review of *Hyg. Lab. Bull.*, No. 87, says in part: "In the period covered by this, the seventh in the series of 'Digests,' the critical character of the comments on the German Pharmacopœia might be taken to indicate that the makers of pharmacopœias must in the future cater to a more and more discriminating constituency. This attitude on the part of users of pharmacopœias is still further emphasized by the growing demand for a limited materia medica and, by inference, the limitation of the scope of the pharmacopœia to substances of recognized therapeutic efficacy and substances which, to some degree at least, lend themselves to adequate standardization, whether chemical or physiologic.—*J. Am. M. Assoc.*, v. 61, p. 2005.

**JAPANESE PHARMACOPŒIA.**—A new revision of the monographs of the Ph. Japon III is announced as taking effect December 27, 1913. The changes involve acetylsalicylic acid, lanolin and oil of sandalwood.—*Chem. and Drug.*, 1914, v. 84, p. 167.

PH. BRIT.—The British Pharmacopœia Committee reports that "Two further sections of the text of the new Pharmacopœia have been prepared by the editors, and have been submitted to the Committee and to the several Committees of Reference. All the sections so prepared have been sent to press and are at present in type, undergoing revision. It is hoped that the appendix, and the concluding parts of the draft, will be ready for consideration early in the new year."—*Pharm. J.*, 1913, v. 91, p. 849.

PHARMACOPŒAL DOSES.—An editorial, in commenting on a proposition, recently made in the Medical Press of Great Britain, to adjust the strength of tinctures so that the doses of various groups distinguished by prefixing "per" and "sub" would be the same, says: "Pharmaceutically the strength of tinctures is only of importance when regarded from the point of view of providing sufficient menstruum adequately to exhaust a drug." "In regard to the suggestion as to names the question arises in connection with sub-tinctures, will the alcohol or the drug in the tincture be the more grateful and comforting to the patient?"—*Chem. and Drug.*, 1914, v. 84, pp. 19-20.

PROPRIETARY MEDICINES IN GREAT BRITAIN.—Xrayser II, commenting on the first year of medical benefit under the insurance act in Great Britain, asserts that it has brought with it a marked change in the nature of business done by chemists and druggists. One man reports that he will dispense 10,000 prescriptions and upon the whole he is satisfied from the profit realized directly from this source. The increase in the prescription business is further notable for the fact that the trade in proprietaries has considerably decreased and should mean that chemists as a whole are enjoying, and will continue to enjoy, the increase in what is after dispensing the most profitable department of their business.—*Chem. and Drug.*, 1914, v. 84, p. 85.

HISTORICAL MEDICAL MUSEUM.—An unsigned article presents a number of illustrations of the Historical Medical Exhibition in Wigmore Street, London, which was organized by Henry S. Wellcome and opened on the occasion of the International Medical Congress during last summer. This museum is now being rearranged as a permanent institution and there is probably nothing in existence elsewhere which is quite like the collection which will shortly be available for the use of students and others interested in the study of antiquarian medicine and surgery. The illustrations include a reproduction of the exterior of a London apothecary's shop of the 17th Century,

"At the sign of 'Ye wild man,'" a reproduction of Liebig's laboratory at Giessen, and the interior of an Italian pharmacy of the 16th Century.—*Pharm. J.*, 1913, v. 91, pp. 944-945.

HISTORY OF PHARMACY.—The *Chemist and Druggist*, January 31, 1914, v. 84, p. 183, announces that an arrangement has been made with the publishers of the "Chronicles of Pharmacy," by the late A. C. Wootton, which enables that journal to offer this book in two volumes at 7s. 6d., carriage paid in the United Kingdom, or 8s. post free to any part abroad. This exceptional offer should popularize the book and make it available to all pharmacists who are in any way interested in the history of their craft. Orders for the volumes should be addressed to the book department of the *Chemist and Druggist*, 42 Cannon Street, London, E. C.

FRIEDMANN INSTITUTES are being organized in various parts of the country and the personnel of these organizations in practically every instance is sufficient to suggest their true nature. Steps have been taken in several states to check this exploitation of the consumptive for commercial gain. But what is most needed is that these unscrupulous attempts should be met with an intensive campaign of education of the public concerning the dangers and worthlessness of this treatment.—*J. Am. M. Assoc.*, 1913, v. 61, p. 1050.

U. S. PATENT FOR A COMPLEX MEDICINE.—An editorial calls attention to U. S. Patent 1,081,069, granted December 9, 1913, for a mixture of excretory constituents—creatinin, guanidin, and allantoin—to be used as a specific in a number of microbial infections and illnesses. The editorial states that the granting of a patent on the claims made should be sufficient to show the need of change in the method of granting patents, at least in the methods governing the issuance of patents for medicinal products.—*J. Am. M. Assoc.*, 1914, v. 62, pp. 54-55.

ALOES.—Tutin and Naunton report an investigation to ascertain if any anthraquinone derivative other than aloe-emodin is contained in aloes. They were unable to isolate such compounds as emodin and chrysophanol but found several samples of aloes which contained aloe-emodin as an impurity.—*Pharm. J.*, 1913, v. 91, p. 836.

ALYPIN, MISLEADING ADVERTISEMENT OF.—Bruck, F., called attention four years ago to the misleading statements in the advertising of alypin. Both an anæsthetic and blood-expelling action are claimed for it but in reality it has none of the latter. It is also stated that alypin is considerably less toxic than cocaine, while Schröder and

others have found that it is fully as toxic as cocaine and the last supplement to the German Pharmacopœia gives the maximum dose the same for both alypin and cocaine.—*Therap. Monatsh.*, Berlin, 1913, v. 27, p. 787.

ARHEOL is a proprietary name for santalol,  $C_{15}H_{26}OH$ , a sesquiterpenic alcohol, the chief constituent of sandalwood. Arheol is a colorless, oily liquid; specific gravity, 0.979 at  $15^{\circ} C$ . It is insoluble in water but soluble in alcohol. It boils under 11 mm. pressure at  $169^{\circ}$ , and under ordinary pressure at about  $500^{\circ} C$ .—*J. Am. M. Assoc.*, 1913, v. 61, p. 1900.

ATOPHAN, SECONDARY EFFECTS OF.—Phillips, John, calls attention to the occurrence of various skin rashes caused by the administration of atophan and reports 5 cases. These rashes resemble those following the administration of antipyrine and indicate that atophan should not be given in the treatment of urticaria as has been advised.—*J. Am. M. Assoc.*, 1913, v. 61, p. 1040.

BEHRING'S DIPHTHERIA VACCINE.—Kissling, K., reports on the application of Behring's new vaccine to immunize children who had been exposed to diphtheria in different wards of the Hamburg general hospital. Of the 310 children treated, 111 were given a second injection and none of this group has contracted diphtheria, and only 8 among the remaining 199. In these cases the patients were convalescing from scarlet fever and the diphtheria was exceptionally mild, or the vaccine did not have time to act before the diphtheria developed; several days are required for the vaccine to complete the immunization. Adults respond with more of a reaction to the vaccine than children. Pre-existing disease of any kind does not seem to be a contra-indication. (*Deutsch. med. Wchnschr.*, 1913, v. 39, No. 51.)—*J. Am. M. Assoc.*, 1914, v. 62, p. 418.

CEREUS GRANDIFLORUS.—Gröber, A. Many contradictory statements have been published as to the activity of *Cactus grandiflorus* and its value as a heart remedy. The pharmacological experiments of the author show that the drug exerts some action on the frog's heart similar to digitalis. This may be attributed to the glucoside present as well as to the alkaloid. The amount of active principles present in the drug is, however, so small, that it cannot be considered in any way as a substitute for digitalis in human therapeutics.—*Therap. Monatsh.*, 1913, v. 27, pp. 580-581.

CHROMIUM SULPHATE.—Kolipinski, S., is quoted as saying: "The diseases in which chromium has been used with success are:



cirrrosis of the female breast, castration, menopause, functional impotency in men, chronic alcoholism, nervous vomiting and vomiting in pregnancy, neurasthenia, locomotor ataxia, exophthalmic goiter and the migraines."—*J. Am. M. Assoc.*, 1913, v. 61, p. 1921.

CUNILA MARIANA L., A SUBSTITUTE FOR SPIGELIA.—Stockberger, W. W. Several samples offered as pink root, recently submitted by dealers in crude drugs, were found on investigation to be spurious and to consist largely of *Cunila mariana* L.—*J. Am. Pharm. Assoc.*, 1914, v. 3, pp. 33-34.

CUSYLOL.—Cusylol is a soluble form of copper citrate, introduced for use in ophthalmic work. It is a blue crystalline powder, soluble about 1:3 in water. The powder is stable. Solutions above 1:1,000 in strength do not keep well, since they attack some kinds of glass with the formation of a flocculent deposit.—*Pharm. J.*, 1914, v. 92, p. 136.

DIGIPAN, according to the manufacturers, represents, with the exception of digitonin, all of the glucosides of digitalis leaves, obtainable by extraction at not exceeding 30°.—*Südd. Apoth.-Ztg.*, 1913, v. 53, p. 833.

DIOGENAL is a new sedative related to veronal. Chemically it is dibrom-propyl-diethyl-barbituric acid,  $C_{11}H_{16}Br_2N_2O_2$ . It is a white crystalline powder melting at 126°. The average dose is 15 grains.—*Chem. and Drug.*, 1914, v. 84, p. 37.

ECHINACEA.—*Anon.* Echinacea has been claimed to be a "specific" for rattlesnake bite, syphilis, typhoid fever, malaria, diphtheria and hydrophobia. Later enthusiasts have credited it with equally certain curative effects in tuberculosis, tetanus and exophthalmic goiter, and with power of retarding the development of cancer. On the basis of the available evidence the Council on Pharmacy and Chemistry decided that echinacea was not worthy of recognition as a drug of probable value. Accordingly it voted not to describe the drug in New and Non-official Remedies (*The Journal*, Nov. 27, 1909, p. 1836). So far as can be learned no reliable evidence for the claims made for this drug has been presented since the Council decided that the available evidence did not entitle it to a place in New and Non-official Remedies.—*J. Am. M. Assoc.*, v. 61, p. 2089.

ELARSON is the strontium salt of chlorarsenobehenolic acid, containing about 13 per cent. of elementary arsenic and about 6 per cent. of chloride. It occurs as an almost white, amorphous, tasteless powder, insoluble in water but slightly soluble in alcohol and ether.

The average adult dose of elarson is 0.008 gm. ( $\frac{1}{8}$  grain), three to five times daily, best taken about an hour after meals.—*J. Am. M. Assoc.*, 1914, v. 62, p. 379.

EMETINE HYDROCHLORIDE.—KORNS, John H. Emetine hydrochloride is the approved method of treatment for amœbic dysentery among missionary physicians in China. In a recent report of 17 cases, 16 did well under the emetine treatment, the 1 exceptional case had been treated unsuccessfully with ipecac powders six months previously.—*J. Am. M. Assoc.*, 1914, v. 62, p. 475.

ERGOT, according to Lieb, owes its pharmacologic action to several constituents; of these, ergotoxine alone is specific. Beta-imidoazolyethylamin, parahydroxyphenylethylamin, and the other sympathoninetic amines are products of the putrefaction which occurs during the manufacture of galenical preparations. Each constituent has a distinct pharmacologic action; stimulation of the uterus is characteristic of them all.—*J. Am. M. Assoc.*, 1914, v. 62, p. 486.

FUCITOL.—Votocek and Potmesil. Fucose, the sugar obtained from bladder-wrack, *Fucus vesiculosus*, when reduced with sodium amalgam, is converted into the alcohol fucitol. This new alcohol crystallizes from ethyl alcohol in silvery leaflets which melt at 153–154° C. Rhodose and fucose are stereo-isomers; and the corresponding alcohols, fucitol and rhoditol, are respectively laevo- and dextro-rotary to the same degree. By mixing the two alcohols in equimolecular proportions in hot alcohol, racemic fucitol is obtained. (*Berichte*, 1913, v. 46, p. 3653.)—*Pharm. J.*, 1913, v. 91, p. 911.

GITONIN.—Windhaus and Schneckenburger have recently separated a new digitalis glucoside from Kiliani's digitonin. Digitonin was dissolved in hot alcohol, 95 per cent. On setting aside the solution for some weeks an amorphous deposit was formed containing the new glucoside. Gitonin is but sparingly soluble in water, in methyl, and in ethyl alcohols. It is insoluble in acetone and in ether. It becomes yellow when heated to 255° C. and decomposes at about 272° C. With sulphuric acid it gives at first a pink, then a red color. The exact formula of the glucoside has not yet been determined; provisionally it is given as  $C_{29}H_{50}O_{23}$ .—*Pharm. J.*, 1913, v. 91, p. 911.

HEDIORITE is the lactone of a-glucoheptonic acid. It is recommended, to the extent of 30 gms. per diem, for diabetic patients. It forms crystals melting at 145° to 148°, easily soluble in water.—*Chem. and Drug.*, 1914, v. 84, p. 89.

HYDROXYPHENYLETHYLAMIN.—The pharmacologic investigation

of synthetic aromatic amines has been greatly stimulated by the discovery of the chemical structure of epinephrine and the demonstration that it belongs in this group of organic compounds. The systematic testing of numerous related and suitably constituted amines has shown that in general they exhibit pressor effects on the circulation and other physiologic phenomena characteristic of the effective agent of the adrenals, their activity increasing according as they approach the chemical structure of epinephrine. One of the most interesting of all these newly investigated products is hydroxyphenylethylamin, which can readily be prepared from the protein cleavage derivative tyrosin by splitting off carbon dioxide from the molecule of the latter. This reaction can be brought about by putrefactive bacteria; and in truth hydroxyphenylethylamin has been detected among the products of putrefaction of proteins and identified by Barger among the pressor principles yielded by putrid meat.—*J. Am. M. Assoc.*, 1914, v. 62, p. 46.

LACTIC ACID FERMENTS.—Puckner, W. A. The frequently made assertions that the lactic acid preparations on the market are worthless, led to an examination of the available commercial products. This examination showed that while all products containing living bacteria are bound to deteriorate, the preparations examined were in viable condition, though, as was to be expected, liquid cultures were more active than were the tablet preparations. It was also found that manufacturers of these products are making every effort to insure the dispensing of reliable preparations when they are ordered by physicians.—*J. Am. M. Assoc.*, 1913, v. 61, p. 2084.

LIQUID PARAFFIN.—Peck, J. Wicliffe, calls attention to the widespread use of liquid paraffin for chronic constipation, in different sections of Great Britain, and to the possibility of developing the sale of this article as a specialty. He also points out that there is a great difference in the viscosity of the many samples obtained and that it is preferable to use one having a medium specific gravity. The more fluid ones are not so useful in the treatment of intestinal stasis and the heavier preparations are apt to be objectionable because they do not easily leave the mouth.—*Pharm. J.*, 1914, v. 92, pp. 28–29.

LIQUID PARAFFIN.—Chrysopathes, J. G. During the Balkan war 920 cases of wounds were dressed with liquid paraffin. In nearly every case the wound healed over in a remarkably short time; even gaping wounds with exposed bones began to heal at once. The oil, in fact, is recommended as a dressing for sores of all kinds, and

where there is severe suppuration the addition of 2 per cent. of iodoform improves matters. (*Zentralbl. für Chirurg.*, Leipsic, November 8, 1913.)—*Pharm. J.*, 1914, v. 92, p. 6.

OPIMUM.—Mr. Jewel, the American Consul at Vladivostok, reports that poppy culture was introduced into the Ussuri district by Chinese, and in 1907 the exports to China amounted to 7223 lbs. This has since increased.—*Pharm. J.*, 1914, v. 92, p. 79.

ORGANIC SILVER SALTS.—Rogers, L. With the exception of argyrol, all of the organic silver compounds tested had a decided bactericidal action against the dysentery bacillus when dissolved in water, being effective in five minutes in dilutions of 1 in 2500 and upwards. In the presence of a little broth, however, their action was always weaker, but in a variable degree.—*J. Am. M. Assoc.*, 1914, v. 62, p. 412.

● PERHYDRIT is a combination of hydrogen peroxide with urea, marketed in the form of 1 gm. tablets representing from 0.34 to 0.35 per cent. of hydrogen peroxide and therefore a solid form of hydrogen peroxide which when dissolved in water may be used as a disinfectant.—*Siidd. Apoth.-Ztg.*, 1913, v. 53, p. 841.

PHENOLSULPHONEPHTHALEIN is a product of the interaction of phenol and sulphobenzoic acid anhydride, differing from phenolphthalein in that a CO group of the latter is replaced by a SO<sub>2</sub> group. Phenolsulphonephthalein is used for determining the functional activity of the kidney. When injected intramuscularly or intravenously it begins to be excreted in normal cases in from five to ten minutes. In cases of a deficient functional activity, the first appearance of its secretion is delayed.—*J. Am. M. Assoc.*, 1914, v. 62, pp. 297-298.

PHENOVAL is a-brom-isovaleryl-paraphenetidin, (CH<sub>3</sub>)<sub>2</sub>CH.CHBr.CO.NH.C<sub>6</sub>H<sub>4</sub>.OC<sub>2</sub>H<sub>5</sub>. It is a new crystalline compound melting at 149° to 150°, and is recommended as sedative and hypnotic. It is insoluble in water, but is soluble in the usual organic solvents. Its dose is from 0.5 to 1.0 gm.—*Chem. and Drug.*, 1914, v. 84, p. 89.

PIKRASTOL, administered in cases of epilepsy, is dimethyloldiformyl-methyleneyl-tetramethylene-pentamine, C<sub>9</sub>H<sub>17</sub>N<sub>5</sub>O<sub>4</sub>. It is amorphous, and does not appear to have a well-defined melting point.—*Chem. and Drug.*, 1914, v. 84, p. 37.

QUININE.—MacGilchrist, A. C., claims that precipitated quinine base is the best all-round form in which to administer quinine by mouth; it can be administered intravenously, and it is preferable to any quinine salt in cases in which hæmoglobinuria is dreaded. (*Ind.*

*J. Medical Research*, 1913, v. 1, No. 2.)—*J. Am. M. Assoc.*, 1914, v. 62, p. 413.

QUININE AND UREA HYDROCHLORIDE.—Cables, H. A., reports eight cases of sciatica treated by hypodermic injections of a four per cent. solution of quinine and urea hydrochloride in normal salt solution. There were 50 injections in all, but no untoward results other than a little soreness that always follows hypodermic injections. Seven patients received six injections each and one received eight.—*J. Am. M. Assoc.*, 1913, v. 61, p. 2303.

RABIES AND THE PASTEUR TREATMENT.—*Anon.* The work of Pasteur drew the attention of the medical profession and the laity to rabies, which up to that time had apparently been neglected. The fatality among Pasteur-treated patients is less than 1 per cent., while the death-rate for all persons bitten by rabid animals is considered to be from 15 to 20 per cent.—*J. Am. M. Assoc.*, 1913, v. 61, p. 1923.

RADIUM.—A recent census of the quantity of radium salts at present in the various laboratories of the world shows that this does not exceed the equivalent of 7 gms. of metallic radium. From 1899 to 1904, from 13 tons of pitch-blende residuum, it was possible to extract only 2 or 3 gms. of radium. Then a stop was put by law to the export of radiferous material from Austria. Radium has since been extracted in France from much poorer ores containing only from  $\frac{1}{2}$  to 2 mgms. per ton, whereas the Austrian pitch-blende contained quite 100 times as much. Besides its use in medicine, its application in the industries is spreading. Radium has been used in silk factories for de-electrifying the material and the machines. It is possible to realize, with radium, an apparatus for measuring from a distance the potential of a conductor, without contact.—*Pharm. J.*, 1913, v. 91, p. 938.

RADIUM IN AUSTRALIA.—*Anon.* Important radio-active minerals are stated to have been discovered at two places in South Australia. In one of these cases the material as a whole did not contain sufficient uranium and vanadium to be of commercial importance in the crude state, but results of considerable scientific interest are said to have been obtained in the course of the inquiry. The composition of another radio-active ore in South Australia has also been determined.—*Pharm. J.*, 1914, v. 92, p. 115.

SAFFRON.—Holmes, E. M., in a review of the varieties of saffron, points out that although this plant is cultivated in most of the large countries for home use, it is exported from very few and its adulteration from the time of Pliny to the present day expresses

to some extent its scarcity. For more than 1000 and probably 2000 years saffron has held its own as a medicine and as an ingredient in food, and it is hardly to be supposed that this would be the case if it possessed no useful properties.—*Pharm. J.*, 1913, v. 91, pp. 941-943.

SALVARSAN.—Editorial. In salvarsan and neosalvarsan reliance is placed in combinations of arsenic of complex molecular structure. In this form the arsenic is relatively non-toxic, but as in the case of many other compounds, the biochemical agencies of the body may split the complex chemical structures into simpler ones, reducing the non-toxic combinations into products which may be highly toxic to the tissues of the human organism. So long as we are not able to predict with certainty what chemical reactions may take place within the body under various conditions, there will remain more or less risk connected with the administration of drugs so potentially toxic as are these higher compounds of arsenic. For future guidance, all instances of unfavorable outcome after their use should be recorded in detail with great care.—*J. Am. M. Assoc.*, 1913, v. 61, p. 2074.

PERMANENT SCOPOLAMINE SOLUTION.—The presence of the higher alcohols, such as mannitol or dulcitol, in solutions of scopolamine, renders them more permanent, and the use of these for this purpose is the subject of a German patent.—*Pharm. J.*, 1913, v. 91, p. 943.

SIAM BENZOIN.—Holmes, E. M., gives an interesting summary of the efforts that have been made in the last 50 or 60 years to find the botanical source of Siam Benzoin. The evidence adduced seems to indicate that the chief, if not the only source of the Siam Benzoin of commerce, is *Styrax Tonkinense*, Craib, which is found in the district between Luang Prabang and Hanoi; second, that the *Styrax benzoides* of Northwest Siam yield a fragrant resin, used locally, but the evidence that it yields any of the Siam benzoin of commerce is not equally satisfactory.—*Pharm. J.*, 1913, v. 91, pp. 804-806.

SPIRIT OF NITROUS ETHER.—Hodgson and Bailey report tests to determine how far the defense usually set up in prosecutions is justified. Results show that spirit of nitrous ether retains its strength remarkably well if kept in small, tightly stoppered bottles and not opened too frequently.—*Pharm. J.*, 1914, v. 92, p. 28.

SYRUPS, FERMENTATION OF.—Cochran and Perkins report an investigation on the influence of small amounts of ethyl alcohol on fermentation in cane sugar syrup, and conclude:

1. One per cent. or less of alcohol markedly accelerates fermentation in syrup of average densities.

2. 1.25 per cent. alcohol has very little influence.

3. Beginning with 1.25 per cent. the presence of alcohol retards fermentation in these syrups, the amount of retardation increasing with the increase in the percentage of alcohol.—*J. Ind. and Eng. Chem.*, 1914, v. 6, p. 141.

THEOFORM.—A condensation product of theobromine with a formaldehyde-liberating substance has been put on the market under the name of theoform. It is claimed to contain 85 per cent. of theobromine, and is therefore richer in that base than diuretin or agurin. A white, bitter powder, soluble 1 : 50 in water at ordinary temperatures, but is not stable in neutral or alkaline solution.—*Pharm. J.*, 1914, v. 92, p. 62.

THYMOLPHTHALEIN occurs in colorless needles, melting at 245–246° C.; readily soluble in alcohol and in acetone; sparingly dissolved by chloroform or by ether. It dissolves in caustic alkalies with the formation of a blue color; it may therefore serve as an indicator for alkalimetry, for the color is not affected by excess of alkali.—*Pharm. J.*, 1913, v. 91, p. 881.

THYROIDEUM SICCUUM.—Bennett, Reginald R., discusses the relative weight of dried and of fresh thyroid gland, and questions the frequently made statement that 1 part by weight of the dried thyroid represents 5 parts by weight of the fresh thyroid. Some observations of his own lead him to believe that the relation is more nearly 1 to 4.—*Pharm. J.*, 1913, v. 91, p. 804.

TYRENE.—Para-iodo-ortho-sulpho-cyclo-hexa-triene pyridine is conveniently shortened for ordinary purposes to tryene. An odorless, non-toxic powder, soluble in hot water, it is introduced as an antiseptic. Specially recommended for use in gynæcology and as a dressing for wounds, either as a dusting powder, gauze or on tampons.—*Pharm. J.*, 1914, v. 92, p. 62.

ULSANIN.—Described as “hydroiodoborate,” is put forward as a new non-poisonous but active disinfectant and healing application for the treatment of wounds. It is a somewhat hygroscopic powder, which, in contact with wound secretions, liberates iodine and oxygen.—*Pharm. J.*, 1913, v. 92, p. 102.

VACCINE.—*Anon.* The virus of variola and of vaccinia is less sensitive to the action of glycerin than bacteria in general, and for this reason it is possible to obtain an almost pure virus of practically

full strength. Prolonged action of the glycerin, however, destroys the virus, but more rapidly at 37° C. than in the cold; if kept at from —5° to —15° C. glycerinated virus may remain active for five years.—*J. Am. M. Assoc.*, 1913, v. 61, p. 2074.

“ZYMASE” IN FERMENTATION TESTS.—Rosenbloom, Jacob. The zymase of yeast can readily be separated by grinding compressed yeast in a mortar with water and sand and adding the expressed liquid to 5 times its volume of alcohol. The precipitate is allowed to settle, filtered and washed with alcohol followed by ether. The precipitate is then dried and preserved in tightly corked amber bottles. Enzyme in this form is still active five months after its preparation.—*J. Am. M. Assoc.*, 1914, v. 62, p. 377.

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### BOOK REVIEW.

E. MERCK'S ANNUAL REPORT OF RECENT ADVANCES IN PHARMACEUTICAL CHEMISTRY AND THERAPEUTICS. 1912. Volume xxvi.

It is not only a pleasure, but pleasure combined with profit to read this annual report devoted to pharmaceutical chemistry and therapeutics; profitable because it keeps one in touch with current literature, and particularly literature from foreign sources, that embraces these two branches of pharmacy and medicine. This is clearly evidenced in the first article which in quite an exhaustive manner deals with Lecithin, 50 pages being required to deal with this organic compound which is so widely distributed in the human and animal organisms, and 21 pages containing references to the literature consulted, making a total of 71 pages.

Preparations and drugs mainly chemicals, and more particularly the action of synthetic chemicals, are commented upon as to their advantages and disadvantages when introduced into the human economy. When attention is called to the fact that this information requires 401 pages one can readily perceive what a wide field is covered.

Organotherapeutics is covered very thoroughly and many interesting things are brought to light in connection with this form of medication.

A supplement to the report contains a very informative paper by Professor Dr. R. Heinz, Director of the Pharmacological Institute of the University of Erlangen on “The Assay and Standardisation of Digitalis Preparations.”

JOHN K. THUM.



## CURRENT LITERATURE.

THE BAD TASTE IN HYPOCHLORITE-TREATED WATER-SUPPLIES.—It is surprising, as pointed out by Lederer (*Proc. Ill. Water Supply Assn.*, 1913, p. 235), that so little attention has been paid to the question of removing the taste from water-supplies treated with chlorinated lime. In this country, especially, where the treatment of many large public supplies has been carried out with brilliant sanitary success, there has been frequent and often bitter complaint about the taste of the treated water. As well known, antagonism has developed in many places between water boards and health departments as a result of these conditions. On one side is the recognition that the danger from water-borne diseases is greatly reduced by hypochlorite treatment: on the other is the necessity of having to bear the burden of daily complaint and to meet the indignant protests of thousands of aggrieved water-drinkers. As pointed out by Lederer, a simple method is available for removing the taste from hypochlorite-treated water. After careful experimenting he has confirmed the advantage of sodium thiosulphite ( $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$ ) as recommended by Bruns. The reaction on the residual chlorin is as follows:  $\text{Na}_2\text{S}_2\text{O}_3 + 8\text{Cl} + 5\text{H}_2\text{O} = \text{Na}_2\text{SO}_4 + \text{H}_2\text{SO}_4 + 8\text{HCl}$ . The acids formed in the neutralization process immediately combine with bases to form neutral salts. Lederer has obtained good results in the elimination of taste in Lake Michigan water treated in this way. Sodium thiosulphate seems to possess marked advantages over sodium sulphite. It must be remembered that the action of the thiosulphate stops the germicidal action of the chlorin so that it is necessary to allow the chlorin to act for a sufficient length of time (Lederer recommends from at least ten to fifteen minutes) before the thiosulphate is added. An interesting point brought out in the discussion of Lederer's paper is that hypochlorite seems under some conditions to accentuate an unpleasant taste originally present in the water. In Toledo, for instance, it is stated that the water develops a disagreeable taste when the river first freezes over, owing to the presence of large amounts of vegetable matter in the water. The bad taste is said to be increased by even small amounts of hypochlorite.—*Jour. A. M. A.*, vol. lxi, No. 16, October 18, 1913, p. 1464.

STUDIES IN CARBOHYDRATES, THE COMPOSITION AND DIGESTIBILITY OF WHEAT BREAD AND ALLIED FOODS, GELATINIZATION OF STARCHES.—In this paper, by Charles H. LaWall, Ph.M., and Sara Graves, B.A., published in Part 2 of the Transactions of the Wagner Free Institute of Science of Philadelphia, are given tabulated observations of the microscopical characteristics of the following starches: Potato, Maranta, Sago, Tapioca, Sweet Potato, Corn, Wheat, Buckwheat, Oat, Rice, Barley, Pea and Bean in the raw state and after having been heated in water to 37°, 80°, and 100° C. respectively, and also after having been subjected to these several temperatures for a period of 30 minutes. Gelatinization points for the various free starches as well as in pastes made from the crushed materials would indicate that in the crushed material the gelatinization points are slightly higher.

• Microscopic studies of the starch as found in bread and crackers, notably in Acme, Freihofer, Sharpless, and Jones breads and in Exton, Sunshine, Educator and Uneeda Crackers, Rolls, Pretzels, and Matzoth are tabulated.

Comparisons of the analyses of the several breads and crackers as given would indicate but very slight differences in these products.

From a comparison of the ten tables included in this paper it is apparent that the food values of the various makes of bread and crackers vary only within very narrow limits and that these variations are largely due to temperature differences.

PHILIP F. FACKENTHALL.

PLEADS FOR DRUG USERS.—A plea for the relief of drug victims was made by Dr. Charles A. Towns, of New York, at a legislative hearing in the New York Legislature at Albany on February 25, on bills designed to restrict the sale of habit-forming drugs, principally cocaine and its derivatives. A feature of the proposed laws is a provision designed to treat those who obtain drugs in violation of the law as victims of disease and not as criminals. This provision would give a magistrate authority to commit habitual users of drugs to hospitals or sanatoriums instead of prison.

# THE AMERICAN JOURNAL OF PHARMACY

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APRIL, 1914

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## THE STERILIZATION OF ADRENALIN SOLUTIONS.

BY L. W. ROWE.

The micro-crystalline active principle of the suprarenal glands, Adrenalin, is quite stable when chemically pure. Since it is a pure principle with a definite chemical formula<sup>1</sup> the powder does not readily decompose when kept under ordinary conditions. However, because of its comparative insolubility in water and its great physiological activity, the preparation most suitable for therapeutic use is a 1 in 1000 solution of Adrenalin Chloride, which is an addition product formed by the action of dilute hydrochloric acid upon Adrenalin. In dilute solutions such as this, the Adrenalin Chloride is readily oxidized, if no preservative is added to the solution and it is exposed to the air. The oxidation and consequently the deterioration of the solution is recognized by the fact that the solution becomes pink, then red and finally brown in color.

Due to this tendency to deteriorate by oxidation, it is claimed that a dilute solution of Adrenalin such as a 1 in 1000 solution would not withstand sterilization by boiling since the heat would naturally tend to hasten the oxidation greatly. The solution is sterile when put on the market, but many physicians wish to make doubly sure by sterilization immediately before use.

The following experiments were carried out with the intention of determining first, how many times a solution of Adrenalin Chloride may be sterilized in a variety of ways without deterioration, and second, the relative stability of such a solution compared with that of a solution of a synthetic product. The latter, with analogous properties and identical composition, is claimed<sup>2</sup> to be more stable than Adrenalin which is obtained from the suprarenal glands.

## FIRST SERIES.

In the first experiment 12 ampoules of Adrenalin Chloride Solution 1 in 10,000 were used. The method of standardization of the solutions which was used in this as well as in all the following experiments was the blood pressure method<sup>3</sup> in which the solution to be tested is diluted till the Adrenalin Chloride content is 1 in 100,000. This dilution is then tested in comparison with a 1 in 100,000 solution which is made up from an accurately weighed amount of C. P. Adrenalin crystals. One ampoule in this series was used as a control and its activity found to be equal to standard. The other eleven were placed in boiling water, one ampoule being removed at the end of each 15 minutes and tested. Each was found to be of standard activity.

• This experiment serves to show that the activity of Adrenalin Chloride Solution in ampoules is not impaired by sterilizing in boiling water for any period of time up to 3 hours.

## SECOND SERIES.

A second lot of ampoules of Adrenalin Chloride Solution was used, one ampoule as before being reserved as a control. The others were sterilized for periods of 15 minutes each and one was removed and tested after each sterilization.

The ampoules for further sterilization were cooled to room temperature before being sterilized again and the process was not repeated oftener than twice a day so that considerable time elapsed between two sterilizations.

Results were as follows:

Ampoule.	Sterilized.	Activity.
No. 1.....	Not sterilized	Standard
No. 2.....	Once (15 min.)	Standard
No. 3.....	Twice	Standard
No. 4.....	3 times	Standard
No. 5.....	4 times	Standard
No. 6.....	5 times	Standard
No. 7.....	6 times	Standard
No. 8.....	7 times	Standard
No. 9.....	8 times	90 per cent.
No. 10.....	9 times	80 per cent.
No. 11.....	10 times	80 per cent.
No. 12.....	11 times	80 per cent.

These results show that ampoules of Adrenalin Chloride Solution can be sterilized a number of times (in this series 7 times) without any deterioration, and after that the loss of activity is gradual.

### THIRD SERIES.

The next experiments give a comparison of the stability of Adrenalin Chloride Solution 1 in 1000 with that of an analogous synthetic substance of equal physiologic activity. The latter was made by treating the crystals with dilute hydrochloric acid and diluting 1 in 1000. The Adrenalin Chloride Solution used was made from C. P. Adrenalin crystals and contained no preservative other than a slight excess of hydrochloric acid. This solution was tested and found to possess standard activity.

Three different procedures were followed in sterilizing the solutions but the conditions were duplicated for each solution in order to obtain a direct comparison. The conditions to which the solutions were subjected will be briefly stated and the results placed in the form of a table so as to give a better opportunity for comparison.

In the first method of this series 10 c.c. of the 1 in 1000 solution to be sterilized was placed in a graduated cylinder which was then plugged with cotton, and gradually heated in a water bath to the temperature of boiling water. This temperature was maintained for 15 minutes and at the end of that time the solution was cooled, made up to its original volume if any loss due to evaporation had occurred, and one cubic centimeter removed for testing. This process was repeated four times.

In the second method 25 c.c. of the solution to be sterilized was placed in a tightly corked bottle which was then partially immersed in boiling water for periods of 15 minutes each. Under these conditions there was no loss by evaporation. Each solution was submitted to four periods of sterilization and a test of its activity made after each period.

In the third method of this series 20 c.c. of the solution to be tested was placed in a small open flask and boiled over a flame for 5 minutes. After each period of boiling the loss due to evaporation, which was considerable, was made up with distilled water and the activity of the solution then determined.

The results of the above experiments were all checked and are summarized in the following table:

	Solution of Adrenalin Chloride.				Solution of Synthetic Substance.			
	1st ster. per cent.	2nd. per cent.	3rd. per cent.	4th. per cent.	1st ster. per cent.	2nd. per cent.	3rd. per cent.	4th. per cent.
First Method: Cotton plugged tube in boiling water 15 minutes at a time.	1. 100	100	90	80	1. 100	100	80	80
Second Method: Tightly stop- pered bottle in boiling water 15 minutes at a time.	1. 100	100	100	90	1. 100	100	70	70
Third Method: Boiled 5 minutes over flame in open flask.	1. 100	100	90	75	1. 100	90	80	75

The results obtained show that Adrenalin Chloride Solution 1 in 1000, containing no preservative other than a slight excess of hydrochloric acid, can be sterilized at least twice by heating to the temperature of boiling water under various conditions without losing any activity. After this the loss is quite gradual, so that it probably would not be noticeable therapeutically until after the fourth or fifth sterilization. By a comparison of the results obtained with Adrenalin Chloride Solution and the solution of the synthetic substance it can be seen that the loss of activity due to sterilization occurs more quickly in the case of the latter solution and also that the deterioration is more marked.

#### SUMMARY.

1. Adrenalin Chloride Solution in ampoules can be heated continuously for 3 hours to the temperature of boiling water without any loss of activity.

2. Adrenalin Chloride Solution in ampoules can be sterilized by immersion in boiling water for seven distinct periods of 15 minutes each without loss of activity.

3. Adrenalin Chloride Solution can be exposed to the air and sterilized at least twice under a variety of conditions without loss of activity.

4. Adrenalin Chloride Solution is more stable than the Solution of a synthetic compound when both are subjected to the same sterilization treatment. The results obtained disprove the statement that the stability of the synthetic exceeds that of the natural product.

#### REFERENCES.

<sup>1</sup> Aldrich: *Jour. Amer. Chem. Soc.*, September, 1905.

<sup>2</sup> Stoll: *Lancet-Clinic*, June 21, 1913.

<sup>3</sup> Houghton: *Jour. Amer. Med. Assoc.*, January 18, 1902.

From the Research Laboratory of PARKE, DAVIS & Co., Detroit, Michigan.

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### NOTE ON THE SOLUBILITY OF PHENOL IN HYDROCARBONS.

By J. D. PILCHER.

Pharmacological Laboratory, School of Medicine, Western Reserve University, Cleveland.

The Pharmacopœia states that Phenol is very soluble in fixed oils. It is less soluble in the mineral oils; as determined in this laboratory one gram of Phenol dissolves in 8-9 c.c. of Petroleum, 20-21 c.c. Petroleum benzine, 45-50 c.c. of Petrolatum liquidum. It is about twice as soluble in solid Petrolatum (1 in 23-24) as in the liquid petrolatum. This difference in solubility of Phenol in the vegetable and animal oils and in the mineral oils is worthy of note for two reasons: In removing Phenol from the skin after accidental application the mineral oils would be less efficacious than the fixed oils, glycerin and alcohol and of little more value than water. However, when the local action is desired, ointments and liquid preparations of Phenol in the mineral oils would be more active than preparations containing the same percentage of Phenol in the animal or vegetable oils, inasmuch as the mineral oils would part with the Phenol more readily than the other oils.

*Methods.*—Weighed amounts of crystallized Phenol were added to the liquid hydrocarbons and allowed to stand, with frequent

shaking, several hours or over night. Small quantities of the oils were then added until the Phenol was completely dissolved. In dissolving the Phenol in the petrolatum the mixture was thoroughly stirred while heating to the melting point; on cooling, the mixture was examined microscopically for Phenol crystals and, when found, the process was repeated with the addition of small amounts of petrolatum until no crystals were visible.

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## RENEWED INTEREST IN PARAFFIN OIL.<sup>1</sup>

By M. I. WILBERT, Washington, D. C.

Within recent years renewed interest is being taken in paraffin oil for internal administration in the treatment of intestinal stasis or chronic constipation. This renewed interest is largely due to the fact that a notable English surgeon, Sir W. Arbuthnot Lane, in his experimental work to prevent the formation of adhesions after surgical interference in the intestinal tract, found that paraffin oil served as an intestinal lubricant and was of material assistance in overcoming persistent constipation.

This use of paraffin oil is by no means new, however, and dates back many years to the introduction of refined petroleum products by Chesebrough and others about 1872.

Previous to this date the residues in petroleum stills had little or no commercial value and were used almost exclusively as lubricants, more particularly axle grease. The possibility of producing an odorless and practically colorless oil and heavier fat by comparatively simple methods, presented the peculiar problem of establishing a market for products of this kind and for some years at least the substances were used largely, if not exclusively, for the adulteration of other fats and oils, and it is this use of vaseline and of vaseline oil as adulterants that later led to experiments to demonstrate their possible food value and the presence or absence of harmful or toxic ingredients. Experiments carried on by N. A. Randolph, Philadelphia, about 1884, not only demonstrated that the heavier petroleum products were not absorbed from the intestinal tract but also showed that they served to act somewhat in the nature of foreign material,

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<sup>1</sup> Presented at the meeting of the City of Washington Branch of the A. Ph. A., March 18, 1914.



and might have some value in the treatment of certain forms of constipation. It was also thought that these products appeared to inhibit fermentation and would, therefore, be of value in the treatment of certain forms of diarrhoea. Some fifteen years later, Robert Hutchinson of England reported practically the same observations and this report led to the then quite extensive use of petroleum and of paraffin oils for various intestinal disorders.

The at one time widespread use of purified petroleum products in the treatment of pulmonary disorders, is, to some extent, traceable to the administration of the naturally occurring petroleum products in various countries and at various times. Crude petroleum has been used from time immemorial as a medicine and perhaps largely because of its disagreeable odor was from very early times used in the treatment of diseases of the respiratory tract. In this country "Seneca oil" had considerable vogue from time to time and was frequently put out in the form of proprietary or "patent preparations" for the treatment of various diseases. After the introduction of purified petroleum products these were offered as substitutes for the formerly used crude oil and, even at the present time, the advertising matter put out in connection with some of the popularly exploited preparations of petroleum do not satisfactorily designate whether or no the crude or the purified product is being advocated.

During the past three or four decades, purified petroleum products have been marketed under scores, if not hundreds, of proprietary names and the misleading claims and statements made in connection with these several preparations are far from being a credit to the owners or to the persons who act as distributors for the several articles. That there is some element of truth in the claims that have been made for petroleum products is evidenced by the fact that the use of petroleum, crude and refined, has persisted in all parts of the world and has at times, like the present, reached amounts that were quite considerable.

With the renewed interest in paraffin oil that is in evidence at present, the time appears to be particularly opportune for pharmacists who are willing to assist in making for true progress to do missionary work and to point out to physicians in a rational and sensible way that paraffin oil and other petroleum products, while they may be useful, must have limitations, that many of the claims made for the proprietary articles are unfounded and not based on fact, that in the event that the physician does wish to experiment

with the product, non-proprietary oils of high quality are readily available and, finally, that these non-proprietary products can be sold to the patient at a very much lower figure than can the proprietary article and still yield the retail druggist a more satisfactory profit.

As intimated above, the products that are available at the present time are many, or at least appear to be numerous, because of the varied trade names under which they are offered. On studying the nature of these products, however, it appears that there is no very great difficulty in establishing certain, at times perhaps arbitrary, lines of demarcation between them and identifying them as belonging to one or the other class of commercially available oils readily obtainable by any pharmacist.

The bulk of the available supply of heavy mineral oil comes from two sources and the products differ materially in chemical composition. The American oil is obtained from paraffin base petroleum and consists essentially of hydrocarbons of the methane series having the general formula  $C_nH_{2n+2}$ .

The so-called Russian Oil, obtained largely, if not entirely, from the oil wells in the Baku district, consists chiefly of monocyclic polymethylenes or naphthenes, having the general formula  $C_nH_{2n}$ . These latter products have been described as hydrated aromatic hydrocarbons and while they behave with reagents very much in the same way as do the hydrocarbons of the methane series, they are more readily purified and generally occur in commerce as water white oils that are quite free from fluorescence or odor. The American paraffin or methane oils usually have a distinct color and are seldom quite free from fluorescence or a peculiar dichroic effect that is particularly noticeable when the preparation is viewed by reflected light. Apart from the appearance, however, there is no evidence that the two products differ in their effect on the animal organism and one has perhaps as many advocates and users as the other.

The density of the commercially available products also varies and the fact that it is proposed to extend the present U. S. P. limits of specific gravity, 0.870 to 0.940 at 25°, to read 0.845 to 0.940 at 25° clearly indicates that the members of the present Committee of Revision are themselves not convinced as to the properties that should be inherent in a mineral oil for medicinal use.

The paraffin oils official in the Pharmacopœias of the Continent

of Europe are usually of the denser variety, 0.865 or higher at 15°, but this is probably due to the fact that there the oil is largely used as a basis for ointments and the various other uses are only now being developed.

In this country paraffin oil or, as it is better known, liquid petroleum, has long been in use as a basis for oil sprays in the treatment of affections of the nose and throat and for this purpose the lighter and more limpid oil appears to be preferred. For internal administration Sir W. Arbuthnot Lane prefers the heavier, European type of oil and this is now available in this country and is being introduced by a number of manufacturers and dealers under proprietary titles, to be sold at fancy prices. Even for internal use, however, there appears to be a definite limit to the solid paraffin that an oil can hold in solution and be palatable or readily taken. At comparatively low temperatures some of these oils are nearly solid and even at ordinary temperatures they are so viscid that they do not readily leave the mouth when taken internally.

Up to the present time it is by no means positively established that the comparatively dense or the viscid oil is to be uniformly preferred for internal administration, and the pharmacist can be of service not alone in assisting the physician to determine which of the two products is the preferable one but also in devising methods of administration and preferable flavors to overcome the objectionable taste of the oil, particularly of the denser variety of oil.

One further question that may be discussed briefly is the dose. One firm, the owner of the product most widely used in this country, says:

“Excellent results are obtained by giving the oil in small doses. In mild cases a tablespoonful at night gives prompt relief. In longer standing cases make it almost a part of the diet and give one or two teaspoonfuls just after meals.”

Dr. Lane and many of his followers, on the other hand, give the oil in much larger doses and insist that it be given shortly before meals so as not to interfere in any way with the digestion of food which it probably would if, as proposed above, it were given with or immediately after meals and thereby intimately mixed with the stomach content.

Bastedo, in his book on materia medica, pharmacology, therapeutics and prescription writing, states that the oil is only mildly laxative and should be given in doses of 30 c.c. two or three times

a day. Other authorities advise even larger doses, and Robinson (*Medical News*, 1900, v. 77, p. 56) reports that he frequently administered nearly a pint in a few hours without any indications of discomfort and no untoward results of any kind. Robinson also asserts that he was able to duplicate the experiments reported by Randolph and reclaim all of the oil that was ingested. Some recent German experimenters, however, appear to believe that a part, at least, of the oil is changed or absorbed in the intestinal tract, and while the bulk of it passes through unchanged it is not possible to reclaim absolutely all of the oil as taken. At the present time, the preferred dose is from one to two tablespoonfuls one hour before meals, or from two to four tablespoonfuls on retiring. The oil may be flavored to make it less objectionable, and several authorities appear to prefer administering the product in the form of an emulsion, though others claim that the emulsion is not so satisfactory and does not give the same uniform good results.

In addition to its use internally as a lubricant or laxative, paraffin oil is also given in the form of rectal injections, and is being exploited more recently as a dressing for wounds, both recent and chronic. In connection with chronic ulcers it is being extolled as a dressing to protect the skin around the focus of suppuration. The oil in these cases not alone protects the skin against irritation from oozing, thus warding off eczema, but also keeps the dressings from sticking.

The use of liquid petroleum as a soothing application in the form of a spray to inflamed mucous membranes of the nose and throat is well-known, as is the use of the same product in cosmetics, such as skin creams or pomades, and the use of this product for these several purposes need not be discussed at this time.

In conclusion, then, the object of this communication is to call attention to the renewed interest that is being manifested by medical men in paraffin oil for internal administration, and as an adjuvant dressing for wounds, and to suggest to pharmacists that they acquaint themselves with the properties of the available material for the purpose of pointing out to physicians the nature and the kind of material that is available as well as the limitations that probably exist.

## THE UNITED STATES PUBLIC HEALTH SERVICE.<sup>1</sup>

By JOHN F. ANDERSON, Director Hygienic Laboratory, U. S. Public Health Service, Washington, D. C.

The Federal Public Health Service is a bureau of the Treasury Department. Beginning as the Marine Hospital Service, through successive acts of Congress it has undergone a process of evolution so that all of its duties are essentially of a public health character, and it is organized with a view to their performance.

The central bureau at Washington, which is presided over by the surgeon-general, has seven divisions, as follows:

1. Personnel and accounts.
2. Foreign and insular quarantine and immigration.
3. Domestic (interstate) quarantine and sanitation.
4. Sanitary reports and statistics.
5. Scientific research.
6. Marine hospitals and relief.
7. Miscellaneous.

Each of the six divisions first mentioned is in charge of an assistant surgeon-general, who is directly responsible for administrative matters in connection with his division. The officer who has charge of the Division of Personnel and Accounts has immediate supervision of the entire personnel and appropriations, and the preparation of the annual estimates therefor.

Through the Division of Foreign and Insular Quarantine and Immigration are administered all matters relating to maritime quarantine and medical inspections of aliens.

Through the Division of Interstate Quarantine are administered all matters relating to the control of contagious and infectious diseases in interstate traffic.

The Division of Sanitary Reports and Statistics handles all matters relating to the collection of morbidity reports, reports of epidemics, and of information pertaining to the geographic distribution of disease and to climate in relation to health and disease.

The Division of Scientific Research administers all matters relating to investigations of contagious and infectious diseases and

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<sup>1</sup> Abstract of a lecture delivered by invitation March 9, 1914, before the Philadelphia College of Pharmacy.

matters pertaining to the public health wherever made. In the field it is represented by the Hygienic Laboratory with its four divisions, the plague laboratory in San Francisco, the leprosy investigation station in Hawaii, the pellagra investigation station at Savannah, Ga., the station at Wilmington, N. C., for the investigation of the parasites of man, and by officers engaged in investigations of typhoid fever, Rocky Mountain spotted fever, poliomyelitis, etc., in different parts of the country, and sanitary surveys of navigable waters wherever conducted.

In the Division of Marine Hospitals and Relief are administered all matters connected with the care and treatment of seamen and recruiting for the several bureaus of the department.

To-day the Public Health Service has a corps of approximately 450 medical officers, 50 pharmacists, and a total personnel of about 2,000.

In the public health law of July 1, 1902, provision is made for annual conferences between the Public Health Service and state boards and departments of health. Provision is also made for special conferences with all or a part of the state health organizations, and upon the application of not less than five state health authorities, a special conference must be called. In effect, there is thus provided an advisory council on administrative matters, which in its development will insure coöperation and be an arbiter on vexed sanitary questions, and in which each state is entitled to representation.

In the same law Congress also provided for an advisory board for consultation relative to investigations to be inaugurated and the methods of making them in the Hygienic Laboratory. By this means the service is brought in touch with the great scientific laboratories, and may avail itself of advice from the highest sources.

Congress has thus made provision for councils in respect to both administrative and scientific matters. Their utilization in the highest degree is one of the most important means of development of public-health organization and public-health work.

The necessity for more and more extensive Federal supervision over international traffic was made apparent by repeated epidemics. The first permanent quarantine law, passed April 29, 1878, was a result of the widespread and severe epidemic of yellow fever during the previous year. The passage of the law of February 15, 1893, was intimately associated with the outbreak of cholera in Europe in 1892, and the quarantine act of June 19, 1906, followed the epidemic

of yellow fever in the Southern States in 1905. Under the above-mentioned laws and a few minor ones, there was finally developed the national system of quarantine as it exists to-day—a system, the development of which occupied approximately 100 years.

All quarantine operations in the United States are conducted under the supervision of the Federal Government, and, with two or three exceptions, all stations are conducted by Federal officers.

A long series of immigration laws have been enacted between the periods March 20, 1819, and February 20, 1907, their general objects from a hygienic standpoint being the improvement of the health and comfort of arriving aliens, and the development of a stronger race in the United States.

On arrival at domestic ports, all aliens are required to undergo medical inspection, and for those suffering with disease, hospitals are maintained. This medical inspection is conducted by the Public Health Service.

The administrative procedures in international sanitation having been established, and their further improvement assured, the great public health problems of the Nation are now of an interstate and intrastate character.

The Federal public health statutes are based upon, or are carefully in accord with that clause of the Constitution which gives the right to Congress to regulate commerce between the states. On account of the far-reaching effect of interstate intercourse on our national life, the field for public health activities on the part of the Federal Government is wide.

Under the quarantine act of February 15, 1893, the secretary of the Treasury is authorized to issue regulations for the prevention of the spread of infectious and contagious diseases from one state to another, where the regulations of the states are inadequate. These regulations may be enforced by state and local authorities, but the Federal Public Health Service is authorized to coöperate in their enforcement, and should the states fail or refuse, the President may adopt such measures as in his judgment shall be necessary.

Examples of work of this character that may be mentioned are coöperative measures for the collection and examination of rodents to prevent plague; anti-typhoid campaigns in urban and rural districts, and sanitary surveys of interstate and international waters in relation to the prevention of the spread of typhoid fever.

There is necessity not only of quarantine measures to prevent the

spread of communicable diseases, but sanitary measures to prevent their propagation. These include the sanitation of trains and vessels and the supplies used aboard, the regulation of conditions under which the employees of common carriers work, and the exclusion of dangerous or infected merchandise from transportation.

On account of the relation of epidemics to the hygienic and commercial welfare of the country, the Federal Public Health Service may, under the provisions of the above-mentioned law, assume responsibilities in respect to their control under the direction of the Secretary of the Treasury and the President. In the event of outbreaks of cholera, yellow fever, smallpox, plague, or typhus fever in any part of the United States, the President is also authorized to cause regulations to be issued and enforced to prevent their spread, and an epidemic fund of approximately half a million dollars is appropriated annually for expenditures of the Federal Public Health Service in suppressing epidemics of these diseases.

It is under such authority that the epidemics of yellow fever in the Southern States, the outbreaks of plague in California and our island possessions, and similar outbreaks have been handled.

#### RELATION OF THE PUBLIC HEALTH SERVICE TO PHARMACY.

The reorganization of the Marine-Hospital Service in 1871, under the direction of a supervising surgeon-general, materially broadened the object and scope of the service and evidenced the advisability of extending the work so as to provide for much needed supervision of varied interests relating to the public health.

Of the many activities that were early developed by the service in this connection, few are of more wide-spread importance to the welfare of the public at large, or more intimately connected with the medical efficiency of the service itself, than the efficient control of medicinal substances and active participation and interest in the revision of the Pharmacopœia of the United States. This service has been regularly represented at each decennial meeting of the Pharmacopœial Revision Convention held since its reorganization as a bureau in 1871, and several of the representatives of the Marine-Hospital Service have served as members of the revision committee. The first of the representatives of the service to be elected to serve as a member of the Committee of Revision was a pharmacist, Oscar Oldberg, who was the delegate of the then U. S. Marine-Hospital



Service to the Pharmacopœial Convention in 1880. This service was also among the first of the government services to adopt the pharmacopœia as the standard for its medical supplies and to require that drugs and medicines conform strictly with these official requirements.

In this connection it may also be of interest to point out that this service was the first to systematically use the metric system of weights and measures and that this use of the metric system by one of the government medical services played a very important part in the practical adoption of the metric system of weights and measures in the sixth decennial revision of the Pharmacopœia of the United States.

The use of the metric system of weights and measures was made compulsory in the then "Marine-Hospital Service" by an order signed by the Secretary of the Treasury, John Sherman, in 1878, at the request of Prof. Oldberg, and the steps that led up to the signing of the order are well foreshadowed in the report of the Supervising General, John M. Woodworth, on the operation of the Marine-Hospital Service for the fiscal year 1877, which includes a lengthy report on the adoption of metric system of weights and measures for medical and pharmacal purposes, by Oscar Oldberg, then chief clerk and acting medical purveyor of the United States Marine-Hospital Service.

With the change of name to the Public Health Service, the need for coöperation in improving the available supply of remedies used in the treatment of diseases and the perfecting of the scientific accuracy in pharmacopœial requirements has become more and more appreciated and provisions have from time to time been made for active coöperation in the work of associations interested in the promulgation of the truth regarding the nature of medicines of various kinds. The general importance of this work from a public health point of view had in a measure been foreseen by the inauguration of the Division of Scientific Research and the establishment in the Hygienic Laboratory of a division of pharmacology devoted to the scientific investigation of drugs as they relate to the public health, particularly as to their potency, efficiency and pharmacopœial purity. Also and in a more direct way, by the authorization by law to undertake the supervision and practical control of certain important medicinal products, such as sera and vaccines.

In 1902 Congress passed a law requiring that all persons or firms

engaged in the manufacture and interstate sale of viruses, serums, toxins, and similar products should be licensed by the Secretary of the Treasury for the sale of such products. An inspection has to be made of the stables, methods, etc., of the firm desiring to be licensed and an examination of all their products has to be made in the Hygienic Laboratory. After a consideration of the inspector's report on the firm's plant and the report on the examination in the Hygienic Laboratory of the various products, a license is either issued or declined. In connection with the enforcement of this law the Public Health Service has promulgated certain regulations to govern those engaged in the manufacture of these important therapeutic products and has established standards for the measurement of the potency of some of them.

For a number of years members of the staff of the Hygienic Laboratory have actively coöperated in the work of the Council on Pharmacy and Chemistry of the American Medical Association, the Committee on National Formulary of the American Pharmaceutical Association and the Committee on Non-official Standards of that latter Association.

This coöperative work done by members of the staff of the division of pharmacology in connection with these several committees is no doubt familiar to you and need not be specifically reviewed at this time.

The division of pharmacology of the Hygienic Laboratory has also contributed much in the way of coöperative work on the revision of the pharmacopœia and has undertaken the study of a number of problems in connection with the present revision. The results have from time to time been published either in the form of bulletins or in papers contributed to the pharmaceutical or medical journals. Up to date these studies include: The standardization of thyroid products; the standardization of the adrenal gland products, more particularly; the standardization of epinephrine; the physiological standardization of the official preparations of digitalis and of ergot; the possible standardization of tincture of caramel, and comprehensive investigations on the solubility and on the melting point of official chemical substances.

Of even more direct interest to pharmacists as an illustration of the nature of coöperative work done in the Hygienic Laboratory are the publications of the series of "Digest of comments on the Pharmacopœia of the United States and the National Formulary."

This work of abstracting the literature relating to the Pharmacopœia of the United States and the National Formulary was undertaken at the request of the board of trustees of the United States Pharmacopœial Convention, with the sanction of the Secretary of the Treasury, and the compilations have appeared in the form of bulletins covering the literature of the calendar years from 1905 to date. This work has received high commendation from physicians, pharmacists and chemists in all parts of the world. The eminent pharmacognosist, A. Tschirch, in commenting on this work, admits that practical Americans were the first to recognize the importance of conserving intellectual energy in connection with the revision of the pharmacopœia and comments favorably on the comprehensiveness of the "Digest of Comments." Pharmaceutical and medical journals generally have commented favorably on the several bulletins and have uniformly voiced the opinion that these bulletins represent a work of great utility and because of the fact that they bring together with remarkable clearness the public comments on pharmacology and materia medica and thus form an index of the work of the year such as is not published elsewhere.

In addition to the work done in connection with the pharmacopœial revision and the standardization of drugs and preparations, there has also been published as *Public Health Bulletin* No. 56 a "Digest of the Laws and Regulations in Force in the United States Relating to the Possession, Use, Sale, and Manufacture of Poisons and Habit-Forming Drugs." This is the first complete analytical compilation of the laws on this subject, and provisions have been made to keep the material up to date by the publication of new legislation in Public Health Reports and the reprinting of this material from time to time as separates. The first of these reprints, covering the legislation enacted during 1912 and 1913, is now being distributed.

As an illustration of the relative importance of matters pharmaceutical to public health work, it may be pointed out that of the 90 bulletins published by the Hygienic Laboratory, no less than 39 are of direct interest to the pharmacist, or have some distinct bearing on the practice of pharmacy. In addition to the 7 volumes on the "Digest of Comments," this list includes the very popular bulletin of 122 pages on the Changes in the Pharmacopœia of the United States of America, eighth decennial revision, compiled by Doctors Reid Hunt and Murray Galt Motter, published in 1905.

Six bulletins deal specifically with the physiological standardization of drugs, four deal with the chemical or physical standardization of official substances, nine discuss the use and standardization of antiseptics, disinfectants and germicides, six refer more specifically to sera and vaccines, and six involve comprehensive studies of chemical tests and other problems of interest to pharmacy.

In addition to the work done in the Hygienic Laboratory practical observations of interest to pharmacists are from time to time reported by individual pharmacists attached to the several stations in different parts of the country.

The present corps of pharmacists includes 16 pharmacists of the first class, 24 pharmacists of the second class, and 6 pharmacists of the third class.

Sanitary reports and statistics and the results of scientific investigations are of value only as they are made public and used. Among the publications issued by the Service are the Hygienic Laboratory bulletins, bulletins of the Yellow Fever Institute, Public Health bulletins, the weekly public health reports, and miscellaneous documents. The Hygienic Laboratory bulletins represent the results of scientific investigations conducted in the laboratory. The public health bulletins are popular in character, and are utilized to convey sanitary information to health officials and to the public generally. The weekly public health reports are issued primarily for the benefit of health authorities as an aid in administration.

Another important function of the Public Health Service in relation to the public health, and perhaps the most important one, is the conduct of scientific investigations.

By an act of March 3, 1901, investigations of contagious and infectious diseases and matters pertaining to the public health were given definite status in law. Provision was made whereby laboratory investigations would be systematically carried on. Through this provision and in connection with the enforcement of the quarantine laws investigations have been made in Washington and different parts of the country. In order to comply with the law, however, this work was carried on largely through the Hygienic Laboratory.

By an act of Congress approved August 14, 1912, broader powers were conferred on the Public Health Service to "study and investigate the diseases of man and conditions influencing the propagation and spread thereof, including sanitation and sewage and the pollu-

tion, either directly or indirectly, of the navigable streams and lakes of the United States."

There is thus abundant authority for both laboratory and field investigations by the Public Health Service. As in the past the investigations will be conducted by officers specially trained and with such coöperation as state and local health authorities may be able to render. But in order that the great needs of the country may be met, more men and more money must be provided and the Public Health Service must have the active support of individuals, professional associations, and other organizations to be benefited.

Many highly important problems await solution. Among them may be mentioned the standardization of biologic and other therapeutic products, the determination of the conditions causing pellagra and certain other diseases, the extent of the migrations of tuberculous and other patients from one locality to another, the ascertainment of the influence of artificial illuminants on health, the determination of the relation of housing and other conditions to labor efficiency, and the prescribing of reasonable standards to control stream pollution.

Requests are received daily from all parts of the country for information regarding sanitary problems and methods of handling them. These requests are an excellent indication of the amount and extent of work to be performed in the immediate future. In one section of the country the question of the pollution of streams is pressing for solution; in another, it may be industrial accidents and poisoning; in another, the question of the reduction of infant morbidity; and in still another, the measures that must be taken to eradicate malaria and other communicable disease.

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### LECITHIN.\*

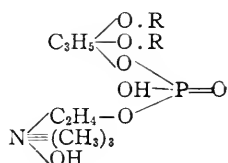
In the economy of living cells belonging to the vegetable and animal kingdoms, a very important part is played by a certain group of bodies, which are generally spoken of collectively as "lipoids."<sup>1</sup>

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\* Reprinted from E. Merck's Annual Report, 1912, vol. xxvi., pp. 1-22.

<sup>1</sup> The word "lipoid" is derived from the Greek *λίπος* = fat. It denotes fatty substances which contain phosphorus, or phosphorus and nitrogen, or neither of these elements, and which have special functions to perform in the cell. An exact definition of the term "lipoid" cannot be given. Kletzinsky

Among the best known members of this group are the cholesterins and lecithins. While the cholesterins are organic combinations free from nitrogen and phosphorus, the lecithins contain both nitrogen and phosphorus. They are grouped together as a special class of bodies, the so-called "phosphatides,"<sup>2</sup> comprising a large number of representatives. The phosphatides are characterized by containing one or more molecules of phosphoric acid, an alcohol (for example glycerin), one or more fatty acid radicles (for example stearic or oleic acid) and one or more nitrogenous bodies (such as choline and allied substances). Lecithin, or rather the lecithins, are phosphatides of this description. The theoretical formula of the lecithins is as follows:



It is highly probable that other substances containing nitrogen and allied to choline may occur in natural lecithin, but so far choline alone has been demonstrated with certainty in the decomposition products of the lecithins. The radicles of stearic, palmitic and oleic acid (R in the above formula) are present in the form of esters with the glycerin radicle in the lecithin molecule. It has not yet been possible to determine whether one molecule always contains either two similar or two different acid radicles. Although in the examination of

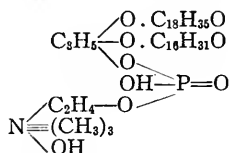
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understood it to mean those substances which cannot be saponified and which may be extracted from animal cells by means of alcohol and ether. If their non-saponification be left out of account, for it applies to cholesterin but not to lecithin, the designation "lipoid" may still be defined in the terms of the author mentioned above, for Overton considers it to denote all those components of the cell which, like fat, will dissolve in ether, chloroform and similar organic liquids. Kraus termed lipoids "noble fats" to distinguish them from fats.

<sup>2</sup> Lecithin is a mono-amino-mono-phosphatide, which denotes that still more complex substances exist, *e.g.*, di-amino-mono-phosphatides, mono-amino-di-phosphatides, di-amino-di-phosphatides, tri-amino-mono-phosphatides, etc. These bodies have not as yet been exhaustively investigated. (Compare Thudichum.)

It should be noted that at the end of the original article in Merck's Report a detailed list of the literature is given, arranged according to authors.

lecithin obtained from egg yolks stearic acid and palmitic acid or oleic acid are usually found, this is not a proof that these acids are derived from a single molecule; for a mixture of stearyl and palmityl-lecithin, or of stearyl and oleic acid-lecithin may equally well be present. But in the text-books of physiology or of physiological chemistry, lecithin from egg yolks is occasionally represented by the assumptive formula of stearyl-palmityl-lecithin:



The structure of this formula may most probably be traced back to the statements of Thudichum; in his opinion a lecithin molecule always contains one saturated and one unsaturated fatty acid residue. According to him, every true lecithin contains at least one fatty acid radicle and always represents a mono-amino-mono-phosphatide,—*e.g.*, the molecule contains only one atom of nitrogen and one atom of phosphorus.

It is generally assumed that the lecithin from egg yolks is mainly stearyl-lecithin and the lecithin obtained from plants mainly oleic acid-lecithin. In how far this assumption is supported by facts cannot be decided on the strength of the researches on the lecithins so far carried out. It is indeed doubtful whether the above formula definitely explains the constitution of the natural lecithins.<sup>3</sup> The investigations of MacLean, Otolski, Cousin, Erlandsen, Henriques and Hansen have shown that the lecithins, besides containing choline, also possibly contain other nitrogenous disintegration products (pyridine) and other unsaturated fatty acids (linoleic acid and linolenic acid). This may also be inferred from the relatively high iodine number of the lecithins, which is not sufficiently explained by their content of oleic acid. Nor can it be decided whether calcium and iron, which always accompany the lecithins, form an essential part of the lecithin molecule or are merely impurities; thus no great weight can be attached to the constitutional formula of lecithin. Further, Malengreau and Prigent, as a result of hydro-

<sup>3</sup> According to Thierfelder and Stern, other phosphatides besides lecithin occur in egg yolks. These have also been found by Thudichum, Hammarsten, Erlandsen and others in various animal organs.

lytic experiments, have expressed doubt as to the possibility of an ester-like combination between choline and phosphoric acid. It is certainly true that the natural lecithins, however carefully they are purified, always represent mixtures of various lecithins. The physical condition of pure commercial lecithin, which is waxy and occasionally somewhat crystalline, is in favour of this view; and it is justifiable to assume, according to the present position of research on lecithin, that the separate lecithins which constitute natural lecithin, in their absolute chemical individuality and purity, are crystalline bodies.

The solution of this problem is, however, of more chemical than physiological or therapeutic interest. As is evident from an investigation by Stepp, those lecithins alone are of physiological or therapeutic importance which are produced by the living organism itself for its own use. It is therefore probably justifiable in therapeutics to speak of pure lecithin when this consists solely of lecithins without admixture of albumins or of lecithalbumins. My *Lecithinum ex ovo purissimum* is a preparation of this nature.

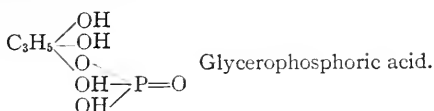
The discovery of lecithin is usually attributed to Gobley (1846), although long before him Vauquelin (1811) and Couerbe (1834) found and described phosphorus-containing fats in the brain, which were probably identical with lecithin. Fremy, a pupil of Couerbe, named Vauquelin's substance "oleo-phosphoric acid," as he found its products of decomposition to consist of glycerin, phosphoric acid and oleic acid. In conjunction with Valenciennes he isolated the same substance from the roe of fish. But Gobley was the first to prepare it from the yolk of eggs, and he called it "*matière visqueuse*," and later, on account of its origin, "*lecithin*," from *λέχιθος* (=yolk of egg).<sup>4</sup> He was also the first to recognise the principal component of lecithin possessing physiological importance, namely glycerophosphoric acid, which is obtained by the careful saponification of lecithin; he thus established the basis for the constitution of the lecithin molecule which is still fairly generally accepted. The basic component of lecithin, choline, was discovered by Liebreich and Strecker.

Lecithin is therefore regarded as a glycerophosphoric acid in

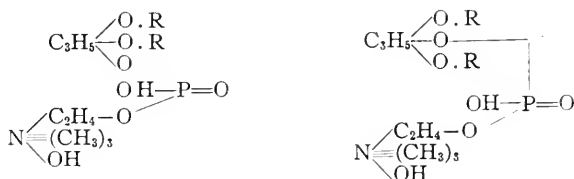
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<sup>4</sup> Strecker's view (*Annalen der Chemie und Pharmazie*, 1868, Vol. 72, p. 77) that the word lecithin is derived from *λίον* (=oil jar) and should therefore be written *lecythin*, is erroneous.





which the hydrogen atoms of the hydroxyls of glycerin are replaced by fatty acid radicles, and one hydrogen of the phosphoric acid residue by a choline radicle. Theoretical consideration shows that two possible formulas exist, one symmetrical and one asymmetrical, according to the position of the fatty acid residues in the glycerin, thus:



Since lecithin is optically active and as, according to Willstätter and Lüdecke and also according to Power and Tutin, the glycerophosphoric acid derived from lecithin possesses rotatory power, Ulpiani expressed himself in favour of the asymmetrical formula. Speculations of this kind are, of course, only of theoretical interest. Possibly the synthesis of the lecithins, which has not as yet been successfully carried out, will throw light on the question of the constitution of lecithin. Hundeshagen, as the result of an unsuccessful synthesis of lecithin, claimed to have proved the truth of Strecker's statement that lecithin was not a salt of di-stearyl-glycerophosphoric acid and choline, but an ester-like combination of the two substances, in which the basic character of choline was retained. The choline salt of di-stearyl-glycerophosphoric acid obtained by Hundeshagen had quite different properties than lecithin. Kade's attempts to prepare lecithin synthetically must also be regarded as failures from a practical point of view.

#### OCCURRENCE OF LECITHIN.

Lecithin is so widely distributed in the human and animal organisms that it has been concluded, though not without contradiction, that no organ exists which does not contain lecithin. Thus the phosphatide is found, according to Hermann, Hoppe-Seyler,

Manasse. Abderhalden and Peritz in the blood; according to Miescher in pus; according to Gobley, Liebreich, Thudichum and Koch in the brain; according to Dunham, Rubow, Krehl, Nerking, Heffter, Baskoff, Noel Paton, MacLean, Bischoff and others in the heart (cardiac muscle), kidneys, suprarenal glands, liver, lungs and spinal cord, and according to Fränkel in the pancreas, muscles, testicles and submaxillary gland as well; according to Chevalier and Koch in nerve tissue (sciatic); according to Glikin, Rolle and Otolski in bone marrow; according to Thudichum, Long and Gephart in bile; according to Dezani, Vacheron and Miescher in the sperm; according to Donath in the cerebrospinal fluid; according to Wallis and Schölberg in ascitic fluid, etc. Further, according to Hoppe-Seyler, it is a component of caviare; according to Burow, Tolmatscheff, Koch, Vageler, Siegfeld, Glikin, Dornic and Daire and Marre it is a component of milk and consequently of butter, as has been proved by Krampelmeyer, Jaeckl and Bordas. The percentage of lecithin indicated by the various authors in human or animal organs is as follows:

Blood 0.2 per cent.

Blood corpuscles 0.46 per cent. (1.8 per cent.)

Brain 16 per cent.

Heart 4.5 per cent.

Cardiac muscle 12.5 per cent.

Kidneys 8.5 per cent.

Suprarenal gland 2.5 per cent.

Liver 4.3 per cent.

Bile 0.15 per cent.

Lung 1.5 per cent.

Spinal cord 11 per cent.

Marrow 3 per cent.

Pancreas 0.5 per cent.

Thymus 7.5 per cent.

Human fat 0.05 per cent.

Muscles 0.8 per cent.

Testicles 1 per cent.

Submaxillary gland 1 per cent.

Nerve tissue 17 per cent.

(of the dry tissue)

Sciatic nerve 33 per cent.

(of the dry tissue)

Sperm 1.5 per cent.

Milk 0.06 per cent.

Butter 0.17 per cent.

Yolk of egg 12 per cent.

Rabbit (living) 0.5 per cent.

Hedgehog (living) 0.8 per cent.

In the vegetable kingdom lecithin is also very frequently found. It was first discovered in plants by Knop in 1860, but its general distribution throughout the vegetable kingdom was first established by Töpler. It is always abundantly present in seeds, buds and young shoots, a fact which indicates its great importance in the growth of

young plants. The lecithin content of various seeds is specially reported upon by Schulze, Forti, Maxwell, Bernardini and Chiarulli; lecithin in vegetable oils by Schlagdenhauffen and Reeb, Stellwaag, Jacobson, Riegel and others; in sugar cane by Shorey; in yeast by Hoppe-Seyler, Himberg and Sedlmayr; in leaves, blossoms, fruits, etc., by Vageler; in fungi by Heinisch, Zellner and Lietz; in grape pips and wine by Rosenstiehl, Funaro and Barboni, Muraro, Biciardelli and Nardinocchi, Salvadori and Mazzaron; and the occurrence of lecithin in the vegetable kingdom generally by Kraetzschmar, Heckel and Schlagdenhauffen, Stoklasa, Hanai, Marchlewski, Winterstein and Hiestand and others.

The content of various seeds, vegetable oils, etc., is given as follows in the literature:

Barley 0.7 per cent.	Cantharellus cibarius 1.3 per cent.
Wheat 0.6 per cent.	Lettuce 0.36 per cent.
Rye 0.6 per cent.	Rhubarb 0.33 per cent.
Peas 1.2 per cent.	French beans 0.25 per cent.
Lentils 1 per cent.	Green peas 0.15 per cent.
Beans 0.8 per cent.	Green tomatoes 0.25 per cent.
Linseed 0.9 per cent.	Yeast (dry) 2 per cent.
Vetch seeds 1.2 per cent.	Wine 0.03 per cent.
Lupin seeds 2 per cent.	Fat of melon seeds 0.6 per cent.
Pumpkin seeds 0.4 per cent.	" " lupin seeds 7.5-50 per cent.
Poppy seeds 0.25 per cent.	" " peas 30-50 per cent.
Maize 0.25 per cent.	" " vetch seeds 13-21 per cent.
Soya-bean oil 0.15 per cent.	" " rye 8 per cent.
Ergot 1.7 per cent.	" " wheat 7 per cent.
Toadstools 1.4 per cent.	" " barley 7 per cent.
Yellow boletus 0.6 per cent.	" " oats 11.5 per cent.
Mushrooms 0.9 per cent.	" " fenugreek seeds 1.5 per cent.
Morel 1.6 per cent.	" " maize 1.5 per cent.

However, lecithin does not only occur as such, but especially in plants in combination with other substances. Thus ovo-vitellein, described by Hoppe-Seyler, is a combination of lecithin with albumin; jecorin, described by Drechsel, Boskoff, Erlandsen and others, is a combination of lecithin with glucose or galactose and other substances; and protagon, which occurs in the central nervous system and in the brain and has been investigated and described by Liebreich, Hoppe-Seyler, Diakonow, Strecker, Gamgee, Blankenhorn,

Baumstark, Ruppel, Kossel and Freytag, is a combination of lecithin with cerebrosides.<sup>5</sup> Protagon is described by Kossel, Ruppel and others as a crystalline substance, soluble in hot alcohol and which swells up in water.

#### PHYSIOLOGY OF LECITHIN.

Special attention has been paid to the study of the origin and significance of lecithin in the vegetable world by Maxwell, Stoklasa, Staniski, Marchlewski, Hanai and Koch. Even though the results of their investigations have not rendered the chemistry of lecithin formation as clear as might be desired, yet they have shown that lecithin may and usually does occur in all parts of plants. From this fact alone it may be concluded that it is a very important or indispensable body in the plant.

Maxwell attempted to prove that the phosphorus present in seeds in an organic form was changed during germination to the organic form, during which process lecithin was produced. The intermediate stages passed through by the phosphoric acid are unknown. In the transition from the vegetable to the animal kingdom the organic combination is, in the author's opinion, retained. The lecithin of a hen's egg, on the other hand, changes when the egg is hatched into inorganic phosphorus compounds, and as a mineral phosphate plays a part in the bone-formation of the developing animal. But in the later stages of hatching, as Maxwell showed, the opposite process may occur. The most interesting fact brought out by Maxwell's researches is that the animal organism is capable of changing inorganic phosphorus into organic compounds. As in the opinion of some observers, to which reference will be made later, the lecithin ingested with the vegetable food is decomposed in the animal intestine and absorbed as phosphoric acid (glycerophosphoric acid), lecithin synthesis must occur in the animal and human organism, for it would otherwise be impossible to explain the origin of the richness in lecithin of the animal organism. Reicher has recently also favoured this opinion.

Stoklasa, from his own observations, formed the opinion that by far the greater part of the phosphoric acid of plants was present

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<sup>5</sup> Cerebrosides are bodies containing nitrogen but no phosphorus, which on hydrolysis produce sugar.

in the form of organic compounds. Besides the nuclein compounds, lecithin is an important example of this class. It probably plays an important part in the processes of assimilation and dissimilation. In testing the lecithin content of seedlings, leaves and blossoms, the author found that the lecithin was not decomposed by germination, but that no lecithin was formed except when, under the influence of light and chlorophyll, carbonic acid assimilation had set in. He even showed that in the absence of chlorophyll (in the leaves) no lecithin is formed and that in etiolated seedlings the lecithin is used up or decomposed. It is possible that during the first vegetative period lecithin, under the influence of light, assists in the formation of chlorophyll in the seedling. The greatest amount of lecithin is probably formed in fresh green leaves at the time when the function of assimilation is at its height, an assumption made probable by the fact that the amount of lecithin in leaf-buds is only half as great as that in fully developed leaves, and that it rapidly disappears as the leaves grow older; the chlorophyll is reduced and xanthophyll makes its appearance. According to this, there is a close connection between the formation of chlorophyll and lecithin. Stoklasa even considers that lecithin may be a product of assimilation in the chlorophyll corpuscle itself. In agreement with this conjecture is the observation that certain plants, if placed in the dark at the time of their most active growth, soon show a considerable diminution of lecithin in their leaves, as compared with those which are allowed to develop in the light. It has not yet been discovered in what way lecithin assists in chlorophyll formation, but according to Stoklasa, it is certain that no chlorophyll can be produced in the absence of light and phosphorus. Thus even if lecithin is not a part of the chlorophyll corpuscle itself, as was formerly assumed by Marchlewski, yet it appears to participate in chlorophyll formation and to supply the necessary phosphorus. From the leaves lecithin travels by way of the stems into the blossoms, where it may perhaps assist in fertilisation, and thence by the fruits into the seeds. It is by no means certain, however, that the green leaves are the sole producers of lecithin; it is quite probable that plants and animals are able to build up lecithin in certain organs and from certain substances, as is the case for example in yeast and in fungi.

Stoklasa's observation that phosphorus is present in plants chiefly in organic form is confirmed by the results of Staniski's researches. This observer found only very small amounts of inorganic phos-

phoric acid in the seeds of millet in comparison with the amount of organic phosphorus present. He found that in millet lecithin formation was at its height during the period of seed development, and that the maximum amount of lecithin was contained in the plant during the period of panicle formation. Thus it is justifiable to draw the conclusion that lecithin has important functions to perform in connection with flower and seed formation.

Hoppe-Seyler pointed out the close relationship between lecithin and chlorophyll mentioned above. He even placed chlorophyll in the group of lecithins. Although this view has not as yet been confirmed, it is supported to some extent by Stoklasa's researches. Furthermore, Marchlewski, Bode and Kohl have put forward theoretical considerations according to which chlorophyll represents a lecithin in which the fatty acid radicles<sup>6</sup> are replaced by special, colored complexes (chlorophyllanic acids), or these complexes themselves are chlorophyll combined with lecithin.<sup>7</sup>

Hanai's statements supplement Stoklasa's communications. He made the observation that the old, green leaves of *Thea Chinensis* lose their lecithin in spring, and that the young, growing leaves are very rich in lecithin. He therefore places lecithin among the reserve substances, which are stored in certain parts of the plant (as, for example, in the bark of the plant just mentioned) until the next period of growth, when they are supplied to the new shoots.<sup>8</sup>

The conclusions drawn by Vageler from his investigations are deserving of special mention. According to these, the lecithins are inseparably bound up with metabolism and with the vital processes of the plant generally. The content of phosphatides increases up to the time of development of the fruit, the zenith of development, and decreases as the fruit ripens. Lecithin has, in the author's opinion,

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<sup>6</sup> Compare the formula for lecithin on page 164.

<sup>7</sup> According to W. Pfeffer (*Pflanzenphysiologie*, 1897, 2nd edition, Vol. I, p. 478), the lecithins are perhaps necessary for the construction of protoplasts. However, it is not yet known whether they take part in the conversion of fats. The occurrence of choline in plants probably depends upon the conversion of lecithin. According to Willstätter, chlorophyll contains no phosphorus, whereby the theories of the authors mentioned above are incorrect. Compare also Marchlewski, *Biochemische Zeitschrift*, 1908, Vol. 10, p. 131.

<sup>8</sup> According to Jost (*Pflanzenphysiologie*, 1908, p. 184), however, the lecithins are not reserve substances, but constructive materials for protoplasm, and for this reason they are not decomposed during germination of the seeds.

probably nothing to do with fat, with which others often consider it to be in relation. Like Koch, he seeks the function of lecithin in the cell primarily as an oxygen carrier, but also in the colloidal character of the phosphatides, "for the substratum of life itself, protoplasm, which is still in many respects so enigmatical, is a colloid."

The physiological significance of the fatty acids contained in lecithin and of choline is explained by Koch. According to him, the lecithins are of importance for the life of the cell in two ways. For in conjunction with the albumins in colloidal solution, they constitute the basis for the formation of the necessary viscosity, on account of the ease with which they are influenced by ions (Na, Ca). Further, by means of their unsaturated fatty acids they take part in oxygen metabolism, and by their methyl groups, which are combined with nitrogen, in other reactions not yet known. Phosphoric acid, although in some respects the nucleus of the whole, does not, in Koch's opinion, play any part in metabolism; Halliburton has shown that the amount of phosphorus in degenerated nerves does not begin to decrease before the eighth day. The author explains the fact that the residues of the unsaturated fatty acids are capable of taking part in oxygen metabolism by the ease with which they are oxidised; this is also known to be the case with lecithin which has been in contact with the air for some time. But it has not yet been proved that the lecithins may be regarded as oxygen carriers. The physiological significance of the nitrogen group may, according to Halliburton, be recognised by the fact that in certain diseases of the nervous system, such as general paralysis, a considerable amount of choline passes into the cerebrospinal fluid.

As in the vegetable kingdom, so in the animal kingdom, lecithin, as I mentioned above, is present in almost every organ. It is present in comparatively large amounts in the principal organs, and the conclusion may consequently be drawn that it also performs important functions in the economy of the animal cell. The nature of these functions cannot be stated with certainty. Nor has it been conclusively ascertained whether lecithin is formed in the animal organism, whether it is ingested with the food, or whether both these processes take place. The results of the investigations of various observers afford some elucidation of the matter.

Bokay found that lecithin was split up in the intestine by the fat-splitting ferment of the pancreas, or putrefactive ferment, into fatty acids, choline and glycerophosphoric acid. As he was unable

to demonstrate the presence of phosphoric acid in ethereal and alcoholic extracts of the fæces, he concluded that lecithin or its decomposition products were absorbed and used up by the organism. In agreement with this conclusion is the fact investigated by him that the amount of phosphoric acid in the urine is substantially increased after the ingestion of lecithin. Glycerophosphoric acid is absorbed from the intestine in the form of a salt, and is not, according to Hasebrök, further broken down into glycerin and phosphoric acid. Grosser and Husler, on the other hand, think it improbable that glycerophosphoric acid passes directly from the intestine into the organism, as they succeeded in isolating a ferment, the so-called glycerophosphotase, from the intestinal and renal cells which splits up glycerophosphoric acid without leaving a residue. They therefore assume that lecithin is completely broken down in the intestine and is built up again from its elements in the tissues. The fatty acids, like the fats taken in with the food, are partially absorbed in the form of salts of fatty acids and partially excreted. Choline is further broken down with formation of carbonic acid, ammonia and methane. As lecithin is said to be comparatively readily broken down, it is probably safe to assume that lecithin is not absorbed as such in the intestine; but this does not prove that it may not be partially absorbed unaltered and carried to the circulation. Miescher's observation on Rhine salmon is generally cited as a typical example of lecithin formation in the animal organism. According to this, a comparatively large amount of lecithin is formed in the sexual organs of these fishes during the hunger period, which is said to occur as they wander up stream. The necessary phosphorus is presumably supplied by certain muscles of the fish. Paton also attempted to prove that in salmon inorganic phosphorus changes into organic phosphorus; however, the assertions of Paton and Miescher can only be accepted if it be proved that during their sojourn in fresh water these fishes really take in no nourishment. This was doubted by Pütter. Röhmman, from experiments on mice, concludes that the animal organism is capable of forming lecithin, for the mice increased and continued their development on lecithin-free food. But in similar experiments carried out by Stepp and Röhl the experimental animals perished. According to Röhl, mice fed exclusively on rice always perish in a few weeks, whereas on the addition of a small amount of lecithin their development continues normally. He therefore con-



siders lecithin to be an essential component of food, which cannot be constructed from its elements in the mammalian body. On the other hand, according to Fingerling's observations, ducks are apparently able to produce large amounts of lecithin from inorganic phosphorus. It must also be assumed that glycerophosphoric acid which has been absorbed is made use of in certain organs for the production of lecithin. The choline required for this purpose has been shown to be present in various parts of the organism (Kinoshita<sup>9</sup>). Mulon, Bernard and others point to the suprarenal glands as the seat of formation of lecithin. Moreover, lecithin appears to be capable of being split up by ferments in certain organs. Coriat, for example, believes an enzyme to be present in the brain, which decomposes lecithin with separation of choline. He did not succeed in isolating this enzyme, but he proved that its action was destroyed by heating.

After Bókay had demonstrated that lecithin could be split up by the secretion from the small intestine, P. Mayer attempted to establish which of the ferments of the small intestine (trypsin, erepsin, lipase) caused this disintegration. He found that lecithin was abundantly split up by steapsin and that under certain conditions the fatty acids separated in a crystalline form. According to this, the behaviour of lecithin is identical with that found by Connstein in the fermentative decomposition of the true fats. Mayer believes his observations to show that the enzymes do not react in the same way upon d- and l-lecithin.

Schumoff-Simanowski and Sieber also confirm the action of pancreatic and gastric steapsin in splitting up lecithin, whereas their tests with lipase of blood or blood serum gave a negative result. It is not capable of splitting off fatty acids from lecithin. It is indeed possible, with the help of this negative character, to distinguish lipase from other lipolytic enzymes. Lecithin is, on the other hand, decomposed by vegetable ferments, especially by the ferment of *Ricinus communis*, with separation of fatty acids.

But the results of the authors mentioned above do not appear to correspond entirely with all the facts, if they are compared with

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<sup>9</sup> Choline is said by Lohmann to occur in the suprarenal glands, by von Fürth and Schwarz in the thyroid gland and intestinal extracts, by Schwarz and Lederer in the thymus, spleen and lymphatic glands, by Kutscher in flesh, by Letsche in serum, by Jacobsen in bile, by Cramer in the brain, by Böhm in the placenta, by Gautrelet in the kidneys, ovaries, testicles and pancreas.

the results obtained by Slowtsoff, Stassano and Billon. According to these authors, lecithin is not by any means readily decomposed and it is doubtful whether it is decomposed by the action of putrefactive bacteria and pancreatic ferment. Thus Stassano and Billon found that neither activated pancreatic juice nor gastric juice acts upon lecithin; this was confirmed by Slowtsoff for fresh lecithin, but he observed the decomposition of older (oxidised) lecithin. He also confirmed the observation that choline was separated from lecithin which had been stored for some time, even when boiled, alkaline ferment solution was used. Independently of the separation of choline, saponification of lecithin by means of pancreatic juice,—*e.g.*, by steapsin, apparently occurs. As lecithin is readily emulsified in the presence of bile and albumoses, and as Stassano and Billon claimed to have observed that lecithin, when injected subcutaneously, ~~was~~ taken up by the leucocytes which had migrated to the site of injection, and that by feeding on lecithin the latter apparently passed into the lymph of the thoracic duct, Slowtsoff conducted experiments which showed that lecithin, when administered internally, is in part ingested unchanged, as could be recognised by the appearance of lecithin in the lymph. As regards the splitting up of lecithin in the intestine, it occurs, according to Slowtsoff, in the duodenum where it cannot, in his opinion, be caused by putrefactive bacteria.

The results of the investigations of the observers mentioned above lead to the assumption that the lecithin taken in with the food is partly absorbed as such and partly split up. Slowtsoff assumes that like the fats it can be gradually reconstructed in the organism by synthesis. The proof of this may be sought in the fact that the same or very similar results have been achieved in therapy with the salts of glycerophosphoric acid (compare Merck's Report 1911, pages 1 to 30) as with lecithin.

With regard to the action on lecithin and its decomposition by ferments (lipase, diastase) reference may also be made to the publications of Lapidus and Terroine.

The investigations carried out by Glikin are of much value for the biological significance of lecithin. He points out that birds and mammals show a greater or less content of lecithin in the bones or the whole body, according as to whether they are born naked and helpless, or independent and with their senses developed. Thus the amount of lecithin in cats and dogs, which are born blind and helpless, is greater than that in guinea-pigs, which immediately after

birth are able to feed on cabbage and turnips like the fully developed animals and are not dependent upon mother's milk; similarly insessorial birds contain more lecithin than autophagous birds, which is indeed clearly shown in the eggs of these birds. Man, also, who comes into the world helpless, shows a very high percentage of lecithin in the bone marrow, which is only appreciably diminished when growth proceeds more slowly, or ceases. He also established the fact that the bone marrow of young animals contains far more lecithin than does that of fully developed animals, and that this store of lecithin diminishes as the animal grows and that newborn animals come into the world with a large supply of lecithin. From these observations it is evident that lecithin represents a highly significant factor in the growth of animals, even though nothing is yet known of the finer biological processes involved in the utilisation of lecithin in the cell and in the organism.

But in order to form a conception of the functions of the lecithins or of the lipoids in general, the colloidal nature of these substances must primarily be taken into account; and also their capability of forming solutions and compounds, which are readily decomposed, with other substances of importance in the construction and the life of the cell. It must also be taken into consideration that certain concentrations of lipoids are more soluble in solutions of alkaline salts than in other salt solutions. It is assumed that by an increase in the concentration of the salt by the entrance of calcium salts into the cell with consequent separation in flakes of the lipoids, membranes are formed which are permeable, impermeable or semi-permeable to certain solutions. The so-called semi-permeable membranes, especially, appear to be of importance to the life of the cell, as they serve to keep within bounds the entrance and exit of substances.

In the interior of the cell, according to Meyer, it is through the intervention of the lipoids that the whole of the contents do not join to form a homogeneous mass, but that the thousand particles forming the cell, with all their different chemical affinities, remain side by side, drawn up in order and at a measured distance; on the surface, however, they constitute a guard against too rapid streaming in and out of water, and against the penetration of all the salts dissolved in the blood and in the tissue fluids, and of other substances. They also form a sort of sieve for the penetration of substances soluble in fat, especially of those which dissolve more readily

in lipoids than in water and aqueous albumin-colloids. The action of narcotic drugs stands in close relation with this solubility in lipoids. It may also be assumed that the functions of the lipoids may, within certain limits, be modified by their different chemical construction and solubility in the body juices, as well as by reciprocal solution. For it is known that the solubility of the best known lipoids, lecithin and cholesterin, may be altered in other fluids by mixing the two substances. Erlandsen found that lecithin, which by itself is insoluble in acetone, became soluble to a slight degree in the presence of cholesterin. It must further be taken into consideration that the lecithin of the organism includes a large number of similarly constructed substances, which occur in mixtures in various proportions, and on account of the varying concentrations of salt solutions are differently influenced and precipitated or redissolved.

• The permeability for albumins and inorganic (calcium, alkali and phosphoric acid) salts of the semi-permeable membranes formed by the lipoids, which is confirmed by the fact that the organic lipoids contain inorganic salts of this kind, facilitates the perception of the electrical processes which, in the opinion of various observers, take place in the cell. Thus Höber and Nernst have developed theories which are intended to explain the connection between galvanic processes in the organ tissues and the stimulation of nerve activity.

The physiological processes which take place in the cells between lecithin and narcotic drugs are of great pharmacological interest. Harlen and von Bibra considered the narcotic action of ether and chloroform to be due to the liberation of fat by these drugs in the cells of the brain. Hermann assumed that the narcotic drugs attacked the lecithins and cholesterins of the ganglion cells. H. Meyer came nearer to the truth when he ascertained that the action of a narcotic drug was the more powerful the more readily it dissolved in lipoids and the less readily it was soluble in water. This was also confirmed by Overton. In his opinion the narcotic drugs pass into those components of the cell which contain cholesterin and lecithin, and alter their physical condition in such a way as to disturb their functions, or to act injuriously upon the functions of other components of the cells. This alteration of function very probably depends upon a sort of anchoring of the narcotic to the lipoids, the bond being weakened by the introduction of other lipoids. This at least follows from Nerking's experiments. This observer administered to animals simultaneously intravenous injections of

lecithin and urethane and found that the usual prompt action of urethane remained absent. He concluded that urethane, injected simultaneously with the lecithin, became anchored to the latter and was thus unable to enter into reciprocal action with the lipoids of the brain. Further experiments with ether, chloroform, morphine, scopolamine, novocaine, tropacocaine and stovaine gave a similar result. The subcutaneous, intravenous and intraperitoneal injection of these narcotics, applied simultaneously with lecithin, always caused an earlier return to consciousness, or the earlier reappearance of sensation. Similarly, animals which had previously received an injection of lecithin required a larger dose of the narcotic than those which had not previously undergone lecithin treatment. These results justify the conclusion that lecithin injections might be employed for human beings also, in order to shorten the period of narcosis or as a prophylactic against its troublesome secondary effects. For experiments of this nature subcutaneous injections of aqueous emulsions of lecithin or intravenous injections of lecithin-sodium chloride emulsions are suitable.

The part played by lecithin in hæmolysis by poisons is also of physiological significance. In 1902 Flexner and Noguchi made the observation that blood corpuscles, which had been completely freed from the adherent serum by washing with physiological salt solution, were not dissolved by snake venom. They assumed that a substance was present in the blood serum which played the part of activator of the amboceptors of the snake venom, and this was later experimentally demonstrated by Kyes. According to Kyes, cobra venom which is inactive towards various kinds of blood immediately assumes hæmolytic properties on the addition of lecithin. If cobra venom occasionally causes solution of blood corpuscles in spite of the absence of serum, it is due, according to Kyes and Sachs, to the lecithin contained in the blood corpuscles; and this occurs more readily the more loosely the lecithin is bound to the blood corpuscle or to the molecule of protoplasm. The communications of Abderhalden and le Count show that the activating properties of lecithin may be arrested by cholesterin.

Finally, the relationship existing between the action of lecithin and that of Röntgen rays or radium rays has gained the consideration of physiologists. Reference may be made to the communications on this subject by Schwarz, Werner, Exner, Sywek, Neuberg, Wohlgemuth and Hoffmann.

## THE IMPORTANCE OF LECITHIN IN METABOLISM AND NUTRITION.

After the favourable effect of lecithin upon phosphorus metabolism and upon nitrogen metabolism had been established, first by Selenski and later by Serono and Charrin, Desgrez and Zaky, experimenting on animals, proved that feeding with lecithin leads to a lasting retention of phosphorus. According to their observations, phosphorus is used for bone-formation and for building up the brain; they were also able to prove that after feeding with lecithin the amount of lecithin in the brain was appreciably increased. The favourable influence exerted by lecithin upon metabolism in general and upon retention of phosphorus in particular, led the two observers to undertake more exhaustive observations on guinea-pigs, in which they found that it was not the glycerophosphoric acid, but the choline which diminished the excretion of phosphorus and causes an increase in the body-weight,—*e.g.*, that the action of lecithin depends upon its basic components. Hatai was able to confirm the favourable influence exerted by lecithin upon growth. He treated white rats belonging to one and the same brood, some with lecithin and some without, and obtained the surprising result that the animals treated with lecithin thrived considerably better, indeed they increased in body-weight by 60 per cent. more than the other animals. Internal administration brought about the best results, but better growth of the animals was also observed after subcutaneous administration.

Danilewski noticed that tadpoles grew with extraordinary rapidity under the influence of lecithin, and he therefore tried the drug in young dogs. He found that the subcutaneous and internal administration of lecithin is a great incentive to bodily growth, improvement of the blood and increase of the brain, which he explains as an acceleration of the bioplastic, morphogenous processes. He observed especially that the dogs treated with lecithin appeared much more lively, more intelligent and physically stronger than the control animals. For his experiments he employed an emulsion of lecithin in physiological salt solution, of which he injected doses of 0.02 to 0.05 gramme of lecithin under the skin of the abdomen, or gave double this dose by mouth. In further experiments on the blood-forming properties of the spleen and the bone marrow, Danilewski and Selenski arrived at the conclusion that lecithin plays an important part in the hæmatopoietic processes which take place in these organs. This assumption gains in probability when it is

borne in mind that lecithin is capable of adsorbing and binding in the organism various substances of importance in the vital process, such as albumins, sugars, salts, ferments, etc., substances which for their part are readily decomposed into their components.

An insight into the relations which exist in metabolism under the coöperation of lecithin is also furnished by the results of the investigations of Franchini, Massaciu, Buchmann, Zuntz, Yoshimoto and Slowtsoff. According to Franchini, feeding rabbits on lecithin increases the lecithin content especially in the liver, less in the muscles and not at all in the brain. The increase in the lecithin content of the liver remains for some time, even after the ingestion of lecithin has been discontinued. The discovery of the author that only very little lecithin is excreted in the fæces tallies with other statements which have been mentioned above. Franchini also confirmed the observation that during lecithin administration an increased amount of glycerophosphoric acid is found in the muscles and in the liver. He also found a slight increase of this acid in the urine, though this may have been first formed from lecithin in the urine, for lecithin is a somewhat labile substance. The fact that no choline could be found in the urine is, however, not in favour of this view.

The choline which is split off from the lecithin during metabolism is, according to the author, further broken down and oxidised in the organism, and appears as formic acid in the urine. Another hypothesis which has not yet been proved has been suggested by Löw. He assumes that lecithin acts in metabolism as a fat-carrier, the fatty acids being split off from the molecule and then replaced by new ones. Part of the lecithin-phosphorus is, according to Yoshimoto and Buchmann, kept back for some time in the organism and is most probably only very gradually excreted. Besides retention of phosphorus, Yoshimoto, Zuntz and Slowtsoff also found retention of nitrogen, which was not always accompanied by an increase in body-weight. Völtz and Massaciu also observed an increase in the albumin content after feeding dogs and guinea-pigs on lecithin, whereas Rogozinski was unable to demonstrate either an increase in nitrogen or phosphorus.

These experiments on animals, the results of which are in part contradictory, have long been rendered perfectly clear by means of the practical employment of lecithin in man. The investigations on metabolism carried out by Cronheim and Müller on several children (under a year old) are interesting. On feeding with children's

meal (consisting of skim milk powder, oatmeal and sugar) and administering lecithin, the nitrogen of the food was better assimilated and retained by the body than was the case when lecithin was not administered simultaneously. In the former case the nitrogen retention amounted to 19 to 28 per cent., in the latter case only to 2 to 24 per cent. On the other hand, as regards phosphorus retention, food containing lecithin showed no advantages, nor could any influence on fat and carbohydrate metabolism be observed. Calcium and magnesium salts were, however, held back by the lecithin, which is a point in favour of increased bone-formation. The older the children, the more evident was the favourable influence of lecithin. This phenomenon is perhaps due to the fact that the body of the suckling contains, according to Siwertzeff, a large store of lecithin, which is gradually used up in the course of the first 4 to 5 months of life. Thus, children under 5 months of age are so richly supplied with lecithin that a further supply becomes superfluous and cannot be utilised. The utility of the drug really first becomes apparent when the store of lecithin has been exhausted.

Recent experiments by Cronheim show that lecithin is not only valuable during growth, but is also of value to adults. A fully developed individual requires a certain amount of lecithin for the maintenance of normal metabolism. It is therefore justifiable to assume that the drug is as beneficial for adults as for children.

Massaciu carried out the following metabolism experiment on a man: he was first given meat and no lecithin, in the second experimental period he received roborat containing lecithin, and in the third period he was given both meat and lecithin. The assimilation of nitrogen was increased threefold in the second period as compared with the first, the nitrogen being better utilised in the intestine. The same occurred in the third period. This furnished a further proof of the nitrogen-sparing power of lecithin. The author also observed retention of phosphorus during lecithin administration. Marfori's results are in agreement with this; he found that egg-lecithin, when subcutaneously applied, furnished the organism with phosphorus capable of being assimilated.

Moricheau Beauchamp experimented on himself and on a medical student and found a nitrogen-sparing and phosphorus-sparing action. The author administered 0.5 to 1 gramme of lecithin a day and found after 4 days that he had gained in energy and that his weight had increased by 900 grammes. In the urine he found a decrease of nitrogen, urea, phosphoric acid and xanthin bodies.



The value of lecithin in nutrition is also shown in a paper by Usuki. The author found in experiments on dogs that lecithin has a favourable influence on the saponification of neutral fat, and that it thus accelerates the digestion of fat. As regards digestion in general, the only doubtful point is whether lecithin exerts a favourable or a harmful influence upon it, or upon the digestive ferments. This point has not yet been settled. Certain conclusions may, however, be drawn from the communications of Hewlett, Fürth, Schütz, Küttner, Kalaboukoff and Terroine. Fürth and Schütz found that bile has the power of augmenting the action of the fat-splitting and albumin-splitting pancreatic ferments, which they consider to be closely connected with the presence of bile salts. Nencki had previously made a similar observation. Hewlett, on the other hand, considered the favourable influence upon these ferments to be due to the lecithin content of bile; Fürth and Schütz were only able to confirm this in the case of an alcoholic solution of lecithin. Küttner attempted to test more carefully the influence of lecithin upon the digestive ferments; he came to the conclusion that definite additions of lecithin sometimes hasten and sometimes delay the enzyme action of gastric or pancreatic juice. He was, however, unable to offer a reliable explanation of the matter. Kalaboukoff and Terroine have expressed the decided opinion that diastatic ferments are not influenced by lecithin. The results of their investigations are as follows: "The addition of lecithin to pancreatic juice never hastens its decomposing action on monobutyrim; it hastens very slightly the action upon oil, but only in relatively high concentrations. The lipolytic action of glycerin extracts of gastric mucous membrane remains unaltered by the addition of lecithin; intestinal lipase is unaltered by the addition of lecithin. The addition of lecithin has no effect upon the rapidity of starch hydrolysis, of digestion of casein and coagulated albumin, or upon the coagulation of milk and pancreatic juice." These results throw doubt upon Hewlett's view mentioned above. The communications of Bang, Wohlgemuth, Lapidus and Starkenstein also show that lecithin does not possess the accelerating action assigned to it by Hewlett.

Slowtzoff, as a result of his lecithin experiments on man, came to the conclusion that lecithin occasioned retention of nitrogen, accompanied by a diminution of sulphuric acid excretion in the urine. He considers this to be related to the decomposition of albuminous bodies, and concludes that what occurs is retention of albumin and not retention of other nitrogenous products (extractives). In his

opinion, the assimilation of albumin runs parallel with the assimilation of phosphoric acid and the diminution of the albuminous substances. This phenomenon shows that lecithin promotes the organisation of albumin,—*e.g.*, its transformation into tissue-albumin. This transition of absorbed into organised albumin must, according to Umikoff and Slowtsoff, be considered as being due to the addition to the albumin of phosphoric acid and xanthin bodies. Thus, according to Slowtsoff, lecithin acts favourably upon this organisation, and it is comprehensible for the increased assimilation of albumin to be accompanied by the retention of xanthin bodies and of phosphoric acid.

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### BOOK REVIEWS.

ALLEN'S COMMERCIAL ORGANIC ANALYSIS. Vol. III. Enzymes, Proteins and Albuminoid Substances, Milk and Milk Products, Meat and Meat Products, Hæmoglobin and Blood, Proteids and Fibroids. Edited by W. A. Davis and Samuel S. Sadtler and the following contributors: E. F. Armstrong, S. B. Schryver, L. L. van Slyke, Henry Leffmann, Cecil Revis, W. D. Richardson, J. A. Gardner, E. R. Bolton, G. A. Buckmaster, W. P. Dreaper and Jerome Alexander. Philadelphia: P. Blakiston's Son & Co., 1012 Walnut Street. 1913. \$5.00 net.

This is another volume of Allen's Commercial Organic Analysis which contains very much matter of special interest to pharmacists. Indeed, every article contains information that is likely to be wanted either for purposes of manufacture or in analytical work. The article on hæmoglobin and its derivatives, by John A. Gardner and George A. Buckmaster, is one of the most succinct articles on the practical examination of blood that we have seen. A similar commendation may be made of the articles on "Proteins of Milk," by L. L. van Slyke, "Milk," by Dr. Henry Leffmann, "Milk Products," by C. Revis and E. R. Bolton, and "Meat and Meat Products," by W. D. Richardson.

In addition to the article on the "Proteins of Milk" there are two other chapters on these highly complex nitrogenous substances. The one on "The Proteins and Albuminoid Substances" by S. B. Schryver and the other on "Proteins of Plants" by J. Frankland Armstrong. While the monograph on plant proteins may not con-

tain as much general information as the work of T. B. Osborne on "The Vegetable Proteins," yet it contains, probably, the essentials for all analytical work.

Among the other valuable articles are those on "Enzymes" by E. Frankland Armstrong and on "Albuminoids in Scleroproteins" by Jerome Alexander. In some respects, this chapter on the albuminoids by Mr. Alexander is one of the most interesting in the whole volume. The word albuminoid is restricted by the biological chemists of America to simple proteins which exhibit pronounced insolubility in all neutral solvents. On the other hand, as many of these protein substances form the chief constituents of the skeleton of animals as well as of the skin and its appendages, the physiological chemists of England apply the term scleroproteins to them. Alexander classifies these substances as follows: (1) Collagens or jelly-forming albuminoids; (2) Fibroids; (3) Chitinoids; and (4) Keratins.

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## CURRENT LITERATURE.

### FORMALIZED GELATIN CAPSULES.

*Enteric Capsules* (Hard and Soft Gelatin).—Used for medicines which are apt to produce gastric disturbance, such as Potassium Iodide, Oil of Santalwood, Sodium Salicylate, Sodium Carbonate, Creosote, Sodium and Zinc Phenolsulphonate, etc.

Ballenger and Elder suggest the immersion of the filled capsule for one minute in a dilution of 1 part of 40 percent. Formaldehyde Solution in from 40 to 60 parts of water. The capsules should be allowed to stand for two weeks after immersion before use.

Another method is to subject the filled capsules to the vapor of Solution of Formaldehyde as follows:

Place the capsules in an open box in a vessel which can be tightly closed. Take 15 Cc. of 40 percent. Formaldehyde Solution for each cubic foot of space in the vessel and pour it on cotton or gauze spread out upon a dish in the vessel.

Six hours' exposure to the vapor is sufficient for capsules which are not to be used immediately. Twelve hours' exposure is preferable for capsules required for immediate use. These estimates are for soft elastic capsules kept at room temperatures (from 70° to 75° F.).

Another plan suggested to secure intestinal absorption is to incorporate the medicament in a mixture of suet and paraffin. The stomach contains no fat digestant and the mass will pass into the intestines. The following combination is suggested:

R	Sodii Carbonatis Monohydratis or	
	Potassii Iodidi or	
	Sodii Salicylatis .....	90 Gm.
	Sevi .....	30 Gm.
	Paraffini .....	16 Gm.
	M. ft. mass.	

Melt all ingredients together on a water-bath and encapsulate in No. 00 gelatin capsules.

To test the efficiency of the method prepare test capsules of methylene blue and oil of santol.

Two hours after administration the eructation following the taking of a carbonated water will indicate whether or not the capsule has broken in the stomach. If the capsules have been hardened too greatly by the formaldehyde, the fact will be indicated by very slow coloring of the urine by the methylene blue.

Mr. Smith, in his Thesis, advises the placing of the filled capsules in a ten percent. solution of formaldehyde during fifteen minutes, then washing them in running water for twenty minutes. The capsules are afterward dried in a dish in a water-bath for five hours or until free from the odor of formaldehyde. They have been used, in his experience, for the administration of Sodium Phenosulphonate and Zinc Phenolsulphonate. (See Thesis of N. L. Smith, P. C. P., 1912, vol. 5; also Ballenger and Elder, in *Jour. A. M. A.*, 1914, p. 197.)

E. F. COOK.

#### DETERIORATION OF NITROGLYCERIN TABLETS.

Rippetoe & Smith (*Journal A. Ph. A.*, January, 1914, 96) report the results of several experiments which lead them to conclude that, "nitroglycerin will volatilize in the process of making the tablets if the granulation is exposed for any length of time, but after compressing the tablets and storing in ordinary corked bottles very little deterioration takes place.

"The tablets will lose in strength if exposed in unstoppered bottles, therefore containers that are not air tight, such as cardboard boxes, should not be used."

The assays were made by the modified Scoville method, which they consider to be a very practical and reliable method.

"Samples of 0.01 (1/100) and 0.02 (1/50) grain hypodermic tablets, which were assayed on April 12, 1912, having been made some time previous, were set aside on a laboratory shelf in ordinary cork stoppered glass tubes of 100 each. These tablets were assayed by the modified Scoville method on November 12, 1913, with the results as shown in the following table:

	April 12, 1912.	November 12, 1913.
0.02 grain	0.0150 grain	0.0149 grain
0.01 grain	0.0061 grain	0.0057 grain

"These tablets while they were deficient in nitroglycerin when made show practically no loss during a period of 19 months.

"A 10 per cent. solution of nitroglycerin (strength was not confirmed by analysis) was mixed with sugar of milk to give a nitroglycerin content of 5 per cent. This mixture upon analysis was found to contain 4.13 per cent. of nitroglycerin. A quantity of hypodermic tablets was made up from this mixture using the theoretical amount based upon the above analysis to give a tablet assaying 0.01 grain. The tablets upon assaying were found to contain 0.0102 grain nitroglycerin. These tablets were handmade while a lot of tablet triturates, which were made from a granulation on a machine using the same quantities as above, assayed 0.0093 grain nitroglycerin.

"Two bottles each containing about 100 of 0.02 grain tablet triturates, made in 1907, were set aside in a closet, one of the bottles being corked and the other having only a piece of muslin over the mouth of the bottle to exclude dust. These tablets were assayed in November, 1913, by the modified Scoville method after having been stored as stated above for six years with the following results:

Tablets in stoppered bottle	0.0130 grain
Tablets in unstoppered bottle	0.0040 grain

"In all probability these tablets would not have assayed, by the modified Scoville method, much over 0.015 grain when made. (Compare assay tablets in first experiment April 12, 1912.)

### WHAT IS SOAP?

Certain resolutions passed at a recent meeting of the Ohio State Pharmaceutical Association regarding the description of soap cer-

tainly need to be accepted with a considerable amount of reservation. Copies of the resolutions passed at the meeting were furnished to the State Authorities of the Federal Department of Agriculture and the Revision Committee of the United States Pharmacopœia and National Formulary.

The following were the actual resolutions adopted:

"Whereas, The market is flooded with various mongrel soaps, masquerading as Castile Soap; and

"Whereas, The Designation Castile Soap has long been recognized as and held to refer to U. S. P. Soap; therefore be it

"Resolved, That we recommend the adoption of such State and National Standards as will forbid the use of the term 'Castile' as applied to any soap other than the U. S. P. Soap; and be it further

"Resolved, That we recommend the incorporation of the term Castile Soap as a synonym for Sapo in the forthcoming Pharmacopœia; and be it further

"Resolved, That copies of these resolutions be furnished to the State Authorities, the Federal Department of Agriculture, and the Revision Committee of the U. S. P. and N. F."

Now we question very much whether the description "Castile Soap" is one that should be maintained at all, and in connection at any rate with British pharmacy it should not be forgotten that the name "Castile Soap" as a synonym for hard soap was abandoned in the British Pharmacopœia of 1898, although it was official in the Pharmacopœia of 1885.

The hard soaps of various Pharmacopœias are described in a variety of ways, and in one case only does the title indicate that the source should be Spanish, namely, the Russian Pharmacopœia, which describes hard soap as Sapo Hispanicus Albus.

The following are the titles employed in the various Pharmacopœias, and we see no reason why the British Pharmacopœia title should not be one generally adopted:

In the United States Pharmacopœia simply Sapo; Belgian Pharmacopœia, Sapo Officinalis; Danish and Dutch, Sapo Medicatus; Hungarian, Sapo Venetus; Norwegian, Sapo Albus Oleaceus; Spanish, Jabon de Sosa; Swedish, Sapo Medicatus; Swiss, Sapo Oleaceus.

It is a pity that in certain works of reference, notwithstanding that the synonym Castile Soap has been officially dropped, the soap should be so described or referred to. For example, in Squire's Com-

panion to the British Pharmacopœia, edition 1908, under the solubility test, reference is made to the digestion of 30 grs. of white Castile Soap in 1 oz. of cold alcohol 90 per cent., when only 24 grs. were dissolved, whilst in the recently published Codex, under Hard Soap, the description is "Hard or Castile Soap," thus assuming that Castile Soap is a synonym for hard soap. It is well recognized in commerce that the soap now supplied as Castile Soap is prepared from a variety of other oils than olive oil.

The resolutions, therefore, that have been adopted by the Ohio Pharmaceutical Association must, in the light of commerce of to-day, be viewed with some considerable amount of reserve. Editorial in "*Perfumery and Essential Oil Record*," September, 1913.

PHARMACEUTICAL EDUCATION.—Dr. H. Thoms writes in a very informative and comprehensive manner on the question of preliminary educational requirements and pharmaceutical training in Germany and other European countries. It is worthy of note that he lays particular stress on the value to a student of a good preliminary education. If he possesses that valuable asset, an asset that is the foundation of success in any calling, he will, other things being equal, be able to overcome what would otherwise seem insurmountable obstacles with ease and facility. It is proverbial that in building operations the stability of the superstructure depends upon a well-laid foundation. So with pharmacy or any of the learned professions.

It is also worthy of observation that the general trend of examinations in determining a candidate's fitness to practise his calling is toward practical laboratory work. Written and oral examinations, combined with practical laboratory work, are the order of the day in Germany as well as in most other European lands. This desirable condition has obtained in Germany for many years, as has likewise the necessity of students possessing a good general education for entrance to the study of a profession.

It does not require a great intellect to see and appreciate the value of further educational development along these lines. It means so much to the general welfare of a community from the stand-point of safeguarding the public health. Men of Thoms's type, both here and abroad, are emphasizing this more and more every day.

Not only is the pharmacist expected, nay, legally required, to stand between the physician and the patient, but he must be able,

in these days when he (the pharmacist) depends to such a large extent upon the manufacturing pharmacist for his pills, tablets, solutions in ampules, tinctures, and extracts both solid and fluid, and other pharmaceuticals, to stand as a bulwark of protection between the manufacturer and the consumer. In other words, the pharmacist is responsible for the purity and accuracy of dosage of all medicines dispensed, whether made by himself or a manufacturing house.

And in order to accept and shoulder this responsibility he must be thoroughly grounded in the principles of the allied branches which comprise the science and art of pharmacy. He must be familiar with and capable of using modern methods and apparatus for the investigation of chemicals and galenical preparations; he must be able to make analyses, both of inorganic and organic chemicals; he also should be able to make microscopical examinations of sections of vegetable drugs and powdered drugs; in short, he should be a pharmacognist; he should be thoroughly conversant with the underlying principles governing bacteriology, as the use of sterile solutions and preparations by physicians is becoming more prevalent every day and it is logical that the pharmacist should be looked to as a source to supply this demand.

Thoms makes it perfectly clear that this development of pharmacy along lines of greater scientific efficiency is not by any means Utopian; that there is great need of better efficiency among the rank and file of the profession, and that it is quite possible and practicable for the student of to-day to receive the necessary training for the realization of this object. If pharmacy is to continue to exist on a scientific basis its proper development must be along a rigorous scientific curriculum.—*Arbeiten aus dem Pharmazeutischen Institut der Universität, Berlin*, vol. x, page 189, 1912.

JOHN K. THUM.

#### RADIUM AND RADIUM SALTS.<sup>1</sup>

Radium is a bivalent metallic element closely related to barium. It is exceedingly reactive, making it difficult to isolate in its metallic state and after isolation to keep in a pure state, as it reacts with air, forming the oxide, nitrite and finally the carbonate. On account of this activity it is only produced in the form of its salts, principally as the bromide, chloride, sulphate and carbonate.

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<sup>1</sup> Jour. Amer. Med. Assoc., January 3, 1914, p. 41.

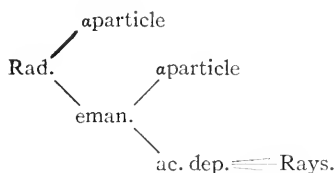


The most important property of radium is its radio-activity upon which depends its therapeutic value. Radio-activity is defined as "the property of spontaneously emitting radiations capable of passing through plates of metal and other substances opaque to ordinary light and having the power of discharging electrified bodies." A spontaneous disintegration of the atoms characterizes all the radio-active elements and it is in this transmutation or splitting of the atom that the rays are shot out, some being material in nature, others electrical or of the nature of light. This spontaneous transmutation of radium is going on at a regular rate, which is independent of the state of combination of radium in the molecule of its compounds.

To determine the radio-active value of radium, use is made of its property of ionizing gases. Thus when radium is allowed to act on the air in a charged gold-leaf electroscope the air becomes ionized and therefore a conductor of electricity and allows the charge to leak out, causing the leaf in the electroscope to move. By observing the rate of movement of the leaf in a calibrated apparatus the radio-activity can be determined.

Quantities and concentrations of radium emanation are expressed in terms of "curies" and Mache units. A "curie" is the amount of emanation in equilibrium with 1 gram of radium; a microcurie, one millionth of a "curie," is the amount of emanation in equilibrium with 0.001 mg. radium and is equivalent to about 2,500 Mache units.

*Relation of Radium, Radium Emanation and Rays.*—The rays are largely derived indirectly from radium through the formation of its "active deposit," according to the following scheme:



These rays are divided into three groups, the alpha, beta and gamma, which differ in their velocity and penetrative power. The alpha and beta rays consist of minute particles of matter electrically charged and moving with a velocity almost equal to that of light. They are for the most part of relatively feeble penetrating power. The gamma rays are vibrations in the ether, very similar to X-rays, and of high penetrating power. Therapeutically the last group is the most useful.

Radium emanation is continuously given off from aqueous solu-

tions of radium salts. It can be collected as it escapes from the solution, drawn off through the use of the mercury pump, or by other suitable means, quantitatively determined by either the alpha or gamma ray electroscope, brought into solution in water for internal or external use or be set free in an emanatorium for inhalation treatment. It may be collected into small glass containers and this used in place of the applicators described under surgical use.

*Actions and Uses:* Radium emanation is said to increase the excretion of uric acid in the urine and to decrease its concentration in the blood; to increase somewhat the number of red blood-corpuscles; to cause temporary leukocytosis early in the course of treatment, the mononuclear increase being relatively greater; to lead frequently through long-continued use to leukopenia, although no appreciable benefit is observed in leukemia. It is said that radium increases general metabolism, and *in vitro* activates certain enzymes, pepsin, pancreatin, rennin, autolytic ferments, tyrosinase and diastase.

It has been claimed that radium emanation is of value in all forms of non-suppurative, acute, subacute and chronic arthritis (luetie and tuberculous excepted), in chronic muscle and joint rheumatism (so-called), in arthritis deformans, in acute and chronic gout, in neuralgia, sciatica, lumbago, and in tabes dorsalis for the relief of lancinating pains. Its chief value is in the relief of pain.

*Surgical Use:* The efficiency of the treatment is due to the beta and gamma rays. The quantity of ray is proportional to the amount of radium element represented in the salt or the emanation. Pure gamma rays may be employed when the apparatus is surrounded by at least 3 mm. of lead. Nearly all pathologic tissues are more sensitive than normal tissues. There is, however, a wide variation in the normal tissues; *e.g.*, the ovary and the sexual organs are very sensitive, the eye and nervous tissues very unsensitive. In skin diseases marked results are obtained with epitheliomata, birthmarks and scars.

*Technic:* Usually heavy doses with epitheliomata, light doses with other conditions. New growths, benign and malignant, of the pelvic organs, the breast, the neck and other parts of the body have been most favorably influenced in some cases. The growths of the mucous membrane of the mouth are quite resistant. There is a remarkable sedative effect in true neuralgia, as well as those due to tumor pressure. The dosage for internal work is heavy, "hundreds of milligrams," and always with the pure gamma rays. The technic

of filtration, of length of application and of amount is still in an experimental stage.

The radium salts and the emanation can be placed in any sealed container, but preferably in glass.

*Dosage:* It may be administered as baths, by subcutaneous injection in the neighborhood of an involved joint (0.25 to 0.5 microcurie in 1 or 2 c.c. distilled water), by local application as compresses (5–10 microcuries), by mouth as a drink cure (in increasing doses of from 1–10 to 10 microcuries three or more times a day), by inhalation, the patient for two hours daily remaining in the emanatorium, which contains 0.0025 to 0.25 (average 0.1) microcurie per liter of air.

#### RADIUM CHLORIDE.

Radium chloride is the anhydrous radium salt,  $\text{RaCl}_2$ , of hydrochloric acid. While nearly pure radium chloride, containing 76.1 per cent. radium (Ra), is said to be obtainable, the market supply is a mixture of radium chloride and barium chloride and is sold on the basis of its radium content.

*Actions and Uses:* See Radium.

*Dosage:* See Radium.

Non-Proprietary Preparation:

*Radium Chloride*, Standard Chemical Co.—Radium chloride is supplied in the form of a mixture of radium chloride and barium chloride for use in radium baths, radium drinking-water and inhalatoriums. It is sold on the basis of its radium content.

Manufactured by the Standard Chemical Co., Pittsburgh, Pa. (The Radium Chemical Co., Pittsburgh, Pa.).

Pure anhydrous radium chloride occurs as a white or slightly brownish crystalline substance, soluble in water.

The presence of radium can qualitatively be demonstrated by electroscopic or by photographic methods.

The quantitative determination of radium is carried out according to the method of Rutherford and Boltwood (Rutherford's "Radioactive Substances and their Radiations").

#### RADIUM SULPHATE.

Radium sulphate is the anhydrous radium salt,  $\text{RaSO}_4$ , of sulphuric acid. While nearly pure radium sulphate, containing 70.2 per cent. (Ra), is said to be obtainable, the market supply is a

mixture of radium sulphate and barium sulphate and is sold on the basis of its radium content.

*Actions and Uses:* See Radium.

*Dosage:* See Radium.

Non-Proprietary Preparation:

*Radium Sulphate*, Standard Chemical Co.—Radium sulphate supplied in the form of a mixture of radium sulphate and barium sulphate for use in applicators. It is sold on the basis of its radium content.

Manufactured by the Standard Chemical Co., Pittsburgh, Pa. (The Radium Chemical Co., Pittsburgh, Pa.).

Pure radium sulphate occurs as a white substance insoluble in water and dilute acids.

The presence of radium may be qualitatively determined by electroscopic or by photographic means.

The radium content may be determined as in the case of radium chloride.

#### WARNING TO USERS OF TURPENTINE FOR MEDICINAL OR VETERINARY PURPOSES.

As the result of an investigation by the U. S. Department of Agriculture, it has been found that the adulteration of turpentine with mineral oils is so widespread that druggists and manufacturers of pharmaceutical products and grocers' sundries should exercise special caution in purchasing turpentine. Those who use turpentine for medicinal and veterinary purposes, unless they are careful, run the risk of obtaining an adulterated article and unnecessarily laying themselves open to prosecution under the Food and Drugs Act.

It has been found, moreover, that the turpentine sold to the country stores especially, as usually put out by dealers and manufacturers of grocers' sundries, is often short in volume by as much as 5 or 10 per cent. Dealers, therefore, should also protect themselves through a guarantee from the wholesaler that the bottle contains the full declared volume.

The Department has found that turpentine may be adulterated in the South where it is made and that the further it gets from the South the more extensively and heavily it is adulterated.

In all cases, druggists, manufacturers and wholesale grocers should satisfy themselves that the turpentine is free from adulteration and is true to marked volume.

# THE AMERICAN JOURNAL OF PHARMACY

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MAY, 1914

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## NOTES ON THE ESTIMATION OF NITROGLYCERINE.

BY F. W. HEYL AND J. F. STALEY.

After abandoning the older nitrometer method for the control of nitroglycerine in pharmaceutical preparations, it was the practice in this laboratory during a considerable period to use in its place the modified Kjeldahl method wherever possible. The Kjeldahl method was found to give results in this instance fully as reliable as in the case of other highly nitrated organic substances such as picrates and picrolonates, which have thus been successfully analyzed.

Recently the latter method has been supplanted in this laboratory by that introduced by Scoville,<sup>1</sup> particularly when preparations bearing minute quantities are under examination. Before abandoning the Kjeldahl method for the superior method of Scoville, we first compared the results obtained by using these two methods in the routine analysis, upon various samples of nitroglycerine preparations. In view of the comparatively large number of collaborators who took part in the coöperative work recently described<sup>2</sup> in the annual report of the Official Agricultural Chemists, the results here given may be of some interest.

In this valuable bulletin the nitroglycerine found by the modified Scoville method is compared with results obtained gravimetrically upon the same sample by extracting with anhydrous ether. It was the experience of some of the collaborators that the gravimetric

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<sup>1</sup> AMER. JOUR. PHARM., 83, 359, 1911.

<sup>2</sup> Bureau Chemistry U. S. Dept. Agric. Bull., 162, 214, 1912.

determination of nitroglycerine was inaccurate, and this would be even more liable to error in anything but the simplest preparations. It is, therefore, of interest to note the comparisons here given of nitroglycerine content as determined by the Scoville method and by the modified Kjeldahl.

Scoville<sup>3</sup> has already briefly compared these values and the figures here given lead to the same conclusions as his, *i.e.*, that the results obtained by these methods are quite alike, and that the variations are due to the difficulties of the methods.

For the analysis of tablets containing minute quantities there can be little doubt that the colorimetric method is both the easier and the more accurate. But in the case of the stock preparations such as the concentrated alcoholic solutions and triturations, the larger quantities of nitroglycerine under analysis make it possible to obtain closely agreeing results by the modified Kjeldahl method. The manufacturing processes can be closely controlled when the stock substances are standardized by the Kjeldahl and the finished product by the colorimetric method, particularly when the conditions are so standardized that a definitely known loss of nitroglycerine, previously determined, is allowed for. Such data are given in the table.

It will be observed, that under the conditions employed for manufacture, the losses of nitroglycerine involved have been reduced to quite narrow limits, averaging about five per cent for moulded tablets and about eleven per cent for compressed ones. Our findings on the compressed tablets are at variance with the losses previously recorded<sup>4</sup>; but this is due to the fact that the tablets are prepared by mixing dry granulations instead of attempting to granulate the mixture. A tablet prepared in this way neither discolors nor loses its strength, and there is no doubt but that a stable standard product results, at least as long as the preparation is properly preserved.

#### EXPERIMENTAL.

For the colorimetric analyses a method equivalent to that outlined in the report<sup>5</sup> of the Official Agricultural Chemists was employed.

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<sup>3</sup> *Loc. cit.*

<sup>4</sup> *AMER. JOUR. PHARM.*, 79, 555, 1907.

<sup>5</sup> *Loc. cit.*

The nitrogen determinations were made as follows: Approximately one gram of the ten per cent alcoholic solution was used for analysis. Where tablets and triturations were analyzed they were first extracted with anhydrous ether, and the ether extracts were evaporated to dryness under reduced pressure at room temperature. The residue was taken up in 1 to 2 c.c. alcohol and collected at the bottom of the flask. Upon this alcoholic solution one gram of salicylic acid was placed and then the Kjeldahl flask was cooled in a freezing mixture. Upon this 40 c.c. of the customary salicylic acid in sulphuric acid solution (previously chilled) was poured and then the mixture was allowed to warm to room temperature, with occasional agitation. The nitration mixture was reduced by the gradual addition of 2 grams of zinc dust, and then the reduction was completed by allowing the reaction to continue for six hours. The mixture was heated gently for five minutes, ten grams of potassium sulphate was added, and the Kjeldahl determination was then finished in the usual manner, using N/20 solutions.

The following table gives the results of analyses on tablets, some prepared experimentally and some commercially:

Preparation analyzed.	Nitroglycerine calculated gm. per tablet.	Found Kjeldahl.	Found Scoville.	Loss, per cent.
1. Nitroglycerine sol.....	.....	9.83% 9.65% 9.66% 9.82% 9.56% 9.71% 9.99% 9.63%	9.75% 9.87%	
2. Nitroglycerine trit.....	.....	10.03% 9.88%		
3. Compressed tablets.....	0.0007744	0.0007228 0.0007039	0.0007044 0.0006843 0.0007083	9.0 11.6 8.6
4. Compressed tablets.....	0.0005194	0.0004557 0.0004768 0.0004546	0.0004540 0.0004508	12.6 13.2
5. Compressed tablets.....	0.0007732	0.0007395	0.0007038 0.0006907 0.0006850	9.0 9.8 9.9
6. Compressed tablets.....	0.0006234	0.0005298 0.0005298	0.0005273 0.0005559 0.0005559	15.4 10.8 10.8
7. Compressed tablets.....	0.0004015	0.0003512 0.0003474	0.0003552 0.0003506	11.5 10.4
8. Moulded tablets.....	0.0006493	0.0006328 0.0006328	0.0006588	0.0
9. Moulded tablets.....	0.000658	0.0006280	0.000616*	6.8
10. Moulded tablets.....	0.0005351	0.0005237	0.0005085 0.0005184	4.9 3.2
11. Moulded tablets.....	0.000720	.....	0.0006830	5.0
12. Moulded tablets.....	0.000688	0.000629	0.0006480	5.9

\* This analysis was made three months after the Kjeldahl.

Since the losses involved in the manufacture of these products must vary with the mechanical details, a brief description of the mechanical conditions employed will suffice. The compressed tablets were usually made in unit runs of 50,000 and the calculated strength in the table was found by taking into account both the waste, which was in each case weighed, and also the over or under run in number. The moulded tablets were made in unit batches of 15,000 and dried artificially in 45 to 60 minutes. All the calculations of loss are based on the colorimetric determinations.

Contribution from the Chemical Research

Laboratory of THE UPJOHN COMPANY.

KALAMAZOO, MICH., March, 1914.

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## THEORIES UNDERLYING THE USE OF ANTITOXINS AND VACCINES.\*

BY A. PARKER HITCHENS, M.D., Glenolden, Pa.

The action of antitoxins has so definitely passed beyond the stage of pure speculation that I think there will be little difficulty in expounding the theories underlying their use. With regard to vaccines likewise we have come to understand more clearly their mode of action without the use of a terminology recognized only by the initiated few.

Out of studies in immunology—the science dealing with the mechanism of contagious diseases—have developed methods by which the body may be assisted either to prevent disease-producing germs from gaining a foothold, or to eliminate them after they have become established.

The disease-producing bacteria are classified in various ways, according to their functions. For our present purpose, the classification of most interest is that which considers the bacteria according to their manner of causing disease. Thus we find that one group of bacteria produces definite, soluble, and diffusible poisons, and that all the symptoms of the disease are directly or indirectly dependent on the action of these poisons upon the tissues for which they have an affinity. The second group of bacteria, on the contrary, does not produce soluble and diffusible toxins in appreciable

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\* Read at a meeting of the American Pharmaceutical Association, Philadelphia Branch, April 7, 1914.



quantity—their effect is brought about by a much more complicated process. We believe the production of disease by this class of bacteria is not a function in which they alone participate, but is the result of their interaction with the body cells.

#### ANTITOXINS.

Belonging to the first class of bacteria, the only organisms of interest to us are the *diphtheria* bacillus and the *tetanus* bacillus. These produce soluble and diffusible poisons—*toxins*; and spontaneous recovery from these diseases depends upon the generation by the tissues of a substance which will neutralize the toxins—*antitoxins*. The requisite antitoxins can be easily produced in animals and transferred to the bodies of patients by administering the blood serum of the treated animals.

For obvious reasons, horses are generally selected for the production of antitoxin. The germs in question are developed upon a fluid artificial culture medium—veal broth. After the bacteria are removed from the full-grown culture, the sterile filtrate, containing the specific toxins, is injected subcutaneously into the horses. The horses react by the production of antitoxin. Enormous quantities of toxin are administered, and consequently enormous quantities of antitoxin are generated and stored in the blood serum of the animal. The antitoxins on the market, then, consist of this blood serum, either native or chemically treated so that the pseudoglobulin constituent of horse serum which carries with it the antitoxic principle is removed and furnished, in solution, in as pure a state as possible.

The strength of the antitoxin is determined by titrating it against toxin, the guinea pig being used as indicator. In defining a unit at present, there is no more reason to say that it is the amount that will neutralize 200 fatal guinea-pig doses of a theoretically pure toxin than there is, in defining an inch, to say that it has a definite relation to the circumference of the earth. Twelve inches make 1 foot, 36 inches 1 yard; 1000 units of diphtheria antitoxin constitute the immunizing dose, 5000 units the average initial curative dose; 1500 units is the official immunizing dose of tetanus antitoxin.

The action of diphtheria antitoxin may be clearly illustrated by imagining the disease to be due to a mineral acid generated within the body and poured into the circulation in constantly increasing quantities. According to the urgency of the case, let us

inject a corresponding quantity of a harmless alkali. The acid is neutralized, the disease is controlled, and the fate of the patient now depends only upon the amount of damage done to the tissues before the alkali was administered.

In tetanus the case is slightly different. Tetanus toxin has a strong affinity for the nerve tissues, and the compound formed by this union cannot be split up by antitoxin. After symptoms of the disease have developed, there is but one hope in treating tetanus with antitoxin. If treatment has begun before the lethal quantity of toxin has been fixed by the nervous tissue, and if the amount of antitoxin then administered be sufficient to neutralize the free toxin in the blood, there is a chance that recovery may ensue.

#### BACTERIAL VACCINES.

For a clear understanding of the action of bacterial vaccines, it may be helpful to consider this subject from the standpoint of our knowledge of anaphylaxis. Anaphylaxis, in its derivation, means a lack of resistance—it is the opposite of prophylaxis. Richet, in his investigation of certain poisons derived from sea urchins, noted that an injection of this poison into a dog, instead of rendering the animal immune to a second dose, actually made him more susceptible. The work of Rosenau and Anderson showed still more clearly the operation of this phenomenon.

Anaphylaxis concerns the effect of proteins or albuminous substances upon animals; it concerns *all* proteins, whether they are poisonous in themselves or not; for instance, egg white and normal horse serum act precisely as the proteins of the plague bacillus or of the typhoid bacillus. And, furthermore, the proteins of dead bacteria act practically in the same way as the proteins of living bacteria. It must be remembered, however, that anaphylactic symptoms can be produced only by proteins foreign to the animal; that is, anaphylaxis cannot occur in a guinea pig from the repeated injection of guinea-pig serum, nor can the symptoms be produced in a horse by the injection of horse serum.

If we inject a guinea pig parenterally—that is, by any route except by the gastro-intestinal canal—it does not appear to suffer the slightest inconvenience. If, however, we inject this animal, two or more weeks later, with the same protein, it will die within one or two minutes and with very definite symptoms accompanying death. This is a manifestation of anaphylaxis.

For an explanation of this phenomenon we must go back to the work of Prof. Victor C. Vaughan upon the chemistry of the protein molecule. Vaughan has shown that a protein, treated chemically according to his method, is split into two parts—the one poisonous, the other non-poisonous. The *poisonous* part obtained from all proteins is the same whether it results from the splitting of egg white or from the splitting of typhoid bacilli; the symptoms leading to death in the guinea pig are identical. This poisonous part, then, is a poison and has no other function or effect; one dose has no bearing upon the effect of a subsequent dose, no hyper-susceptibility is produced, and no tolerance, even by repeated administration.

The *non-poisonous* part, on the other hand, is specific in its action. The non-poisonous part of typhoid bacillus protein will immunize an animal against typhoid infection, but not against infection with colon bacilli; the non-poisonous part of horse serum will sensitize a guinea pig to horse serum, but not to goat or sheep serum.

These results of Vaughan's work upon the chemistry of proteins suggest an explanation of the mechanism of anaphylaxis; they show us that, instead of being the opposite of immunity, anaphylaxis is merely one of its manifestations; and, furthermore, they give us a clearer understanding of immunity itself.

When foreign proteins are injected into the tissues of an animal, the body cells at once set to work to remove this protein. They prepare a ferment capable of splitting the protein molecule, which possibly because of its size is not diffusible, into smaller fractions able to pass into the circulatory system and be thence eliminated. These fractions of the protein molecule are similar to those obtained by Vaughan in his chemical splitting; that is, a *poisonous* part which, after the first injection, is liberated slowly and is therefore harmless in its effect, and a *non-poisonous* specific part which stimulates the body cells to produce a specific ferment-like substance. About two weeks after injection the protein has been entirely removed from the tissues, the poisonous part has been eliminated so gradually that no symptoms have resulted, and the non-poisonous part has stimulated the tissues to generate a large amount of specific protein-splitting ferment.

At this point we must pause to note that, according to Vaughan, the protein-splitting ferment includes the antibodies so difficult to

understand in the theories of the German and French schools of immunity. This theory of the American school does not contradict the fact established by Metchnikoff, and further elucidated by Wright, that the white blood-corpuscles play an active part in the removal of foreign proteins, whether they be cells or fluids; nor is it out of harmony with the theory of Ehrlich, who gives to the group of antibodies—collectively called “the ferment” by Vaughan—different names according to their functions.

The guinea pig, then, at the end of two weeks after the first injection of, let us say, horse serum contains in his tissues no trace of horse serum; but he does have within his body a large quantity of protein-splitting ferment which may remain in the tissues for a long time; and, even if it disappears, the power to generate this ferment upon demand may remain permanently. If we now inject into this guinea pig a second dose of horse serum, the proteins contained therein are at once attacked by the specific ferment; digestion occurs almost immediately, resulting in the liberation of a large quantity of the poisonous part of the protein molecule; the animal is overwhelmed by it and dies usually in less than five minutes. A dose sufficiently large to cause death depends upon the method of injection; if injected into the circulation or into the brain,  $1/20$  c.c. is sufficient; if injected subcutaneously, however, at least 5 c.c. is usually necessary.

Now as to the bearing of this phenomenon upon infectious disease—Vaughan has used typhoid fever as a typical illustration. Infection results from the entrance of a few typhoid bacilli into the tissues under circumstances which permit their growth and multiplication. There is normally present in the body a small amount of a non-specific protein-splitting ferment which attacks the typhoid bacilli, liberating the non-poisonous part, which in turn begins to stimulate the tissues to the production of a specific anti-typhoid ferment. We know that in guinea pigs it takes from eight to fourteen days to produce enough ferment to cause serious symptoms of intoxication upon the injection of a second dose of the protein. Now this period corresponds exactly to the incubation period in typhoid fever. It is during this time that the typhoid protein-splitting ferment is produced in increasing quantities, while the typhoid bacilli are rapidly growing in numbers. The ferment sets free the poisonous part in gradually increasing quantities with the final appearance and progressive increase of fever and the other

symptoms of the disease. This process continues up to the point where the number of typhoid bacilli destroyed each day equals the number reproduced in the lesion. This balance is maintained for a time until the number of bacilli destroyed exceeds those reproduced.

A patient recovered from typhoid fever has remaining in his tissues a large amount of typhoid protein-splitting ferment, so that when typhoid bacilli again gain entrance to his tissues they are at once attacked and destroyed before they have a chance to develop. Obviously there is no intoxication, because the amount of typhoid proteins is infinitesimal compared to the amount necessary to result in anaphylactic shock.

It is now easy to understand the action of typhoid vaccine. When we inject beneath the skin a number of typhoid bacilli, their disintegration is started by the normal proteolytic ferments in the body. A second and third dose given at intervals of about ten days increases the quantity of specific typhoid protein-splitting ferment. The theory of typhoid immunity by means of bacterial vaccines applies equally to the production of immunity to other infecting bacteria. The theory underlying the use of bacterial vaccines in disease is based on the fact that the tissues affected are unable to produce a sufficient quantity of the specific ferment to overcome the infection. The injection of bacterial proteins in a healthy part of the body leads to the production there of these antibodies, which are conveyed to the focus of infection through the circulatory system and thus assist the local cells.

It will now be clear that the requisites to success in vaccine therapy are (1) that the vaccine injected must contain bacterial proteins identical in kind with those causing the infection, (2) that the ferment produced locally must come in contact with the infecting bacteria. For one with proper training it is not hard to determine the kind of bacteria causing an infection; nor is it hard to obtain either a stock vaccine representing these bacteria or to prepare an autogenous vaccine identical with them; and it is a very simple matter to inject these bacterial suspensions beneath the skin of the patient.

If the patient is not in the last stages of disease, there is not one chance in many thousands that his tissues will fail to produce the proper antibodies or ferments. If the patient shows no improvement as result of the treatment, it behooves the physician to use means by which the ferments may be induced to perform their function.

In some infections, as in staphylococcic infection, accessory measures are seldom needed, while in streptococcic infections they are nearly always necessary. In gonococcic infections of the urethra and prostate, the mere injection of vaccines accomplishes but little; in gonococcic infections of the joints, however, the vaccine is apparently sufficient.

We are indebted to Besredka of the Pasteur Institute in Paris for an improvement upon bacterial vaccines which constitutes a real advance in vaccine therapy. As said above, when the bacterial vaccine is injected beneath the skin a small quantity of the protein is split up by natural ferments and the specific non-poisonous part thus liberated stimulates the production of ferments which continue the disintegration until the maximum effect of the vaccine is obtained.

The ferment itself is composed of at least two constituents; one is specific, and by Ehrlich has been called *amboceptor* (the *opsonin* of Wright is a similar antibody). This substance has the power of fixing itself to the bacteria, thus preparing them for digestion by another substance which is not specific but is always present in the blood of healthy animals, and because the latter completes the ferment action it is called *complement*. Besredka proposed that amboceptor be utilized to prepare the bacteria for the immediate action of the complement. The amboceptor is obtained by injecting goats or sheep with massive doses of bacteria like those it is desired to sensitize. Bacteria thus prepared for the action of the complement were said to be "sensitized," and the suspensions of such bacteria were called by him "sensitized vaccines." The advantage they have over ordinary bacterial suspensions is that they eliminate the period during which the specific ferment is being formed. "Sensitized vaccines" have already been used extensively in France and also to a certain extent in England. The published reports amply attest their superiority.

#### ANTIBACTERIAL SERUMS.

The so-called "therapeutic or antibacterial serums" include antistreptococcic, antipneumococcic, and antimeningococcic serums. These are prepared by the injection of horses first with dead and then with living bacteria. In the case of antimeningococcic serum injections of autolyzed bacteria are alternated with the cocci them-

selves. The autolysate contains a toxic substance which causes the production of some antitoxin. This serum, like antidysenteric serum, partakes, therefore, of the nature of both an antitoxic and an antibacterial serum.

These serums depend for their activity upon substances called ferments by Vaughan, but, according to the nomenclature of Ehrlich, "antibodies"; that is, substances antagonistic to the bacteria. Used in sufficiently large doses, antibacterial serums have undoubtedly great value. The chief difficulty lies in the fact that no method has so far been found by which antibacterial serums can be produced comparable in potency with diphtheria antitoxin.

It is well known that a much larger dose of any curative serum must be used if it is injected subcutaneously than if injected intravenously. Realizing this fact and the relative weakness of antibacterial serums, there is but little doubt that their use intravenously will be resorted to in the future with increasing frequency.

#### SUMMARY.

1. There are two classes of bacteria with regard to their method of producing disease: (a) Those that produce soluble and diffusible toxins, and (b) those that do not.

2. The toxin-producing bacteria are the diphtheria bacillus and the tetanus bacillus.

3. Antitoxins produced by injecting horses with the specific toxins are antagonistic to the specific toxic products of the bacilli in a manner very similar to the antagonism between acid and alkali.

4. To the second class belong the great majority of the disease-producing bacteria.

5. The symptoms in the diseases caused by the latter are probably the result of the action of their specific metabolic products combined with the effect of the liberated poisonous part of their protein molecule.

6. Recovery from such infectious diseases depends upon the production of sufficient specific protein-splitting ferment to remove their causative bacteria from the tissues.

7. The amount of this specific protein-splitting ferment may be increased by injecting bacteria of the same kind beneath the healthy skin.

8. Immunity from infectious disease depends upon the existence

in the tissues of sufficient specific protein-splitting ferment to dissolve invading bacteria before they have a chance to develop.

9. The rational administration of bacterial vaccines presupposes accurate diagnosis and the administration of bacteria identical in kind with those causing the infection. It depends, furthermore, upon the ability of ferments and antibodies to come in contact with the infecting bacteria.

10. "Sensitized vaccines" are superior to ordinary vaccines because they reduce the preliminary period during which the injected bacteria are being split up so that the non-poisonous part may be available for the production of specific antibodies.

11. Antibacterial serums—antistreptococcic and antipneumococcic—depend for their activity upon their content in specific antibodies or ferments.

12. The amount of these ferments in even the best serums is relatively small, and the serums must therefore be used in larger doses than has been customary in the past.

13. Antimeningococcic serum is both antibacterial and antitoxic.

14. Since the efficiency of curative serums is increased many fold when administered intravenously, this route will be used more frequently than has been the custom in the past.

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## A CONSIDERATION OF AUTOGENOUS VACCINES.

By B. B. VINCENT LYON, A.B., M.D.

Pathologist to Methodist Episcopal Hospital; Assistant Pathologist to German Hospital, Philadelphia.

Empiricism is dying. Throughout the last century, and particularly its latter decades, the searchlight of truth has lighted up many of the heretofore dark places in the study and practice of medicine. The discovery of the causation of many diseases through bacterial agencies was epoch-making, and led the way naturally toward the introduction of measures able to cope with such a foe.

During the last thirty years scores of men have been at work on this problem and have each added their little to the sum of our present knowledge, and from the time of Jenner one startling etiologic and therapeutic discovery has followed another, so that among the names destined to live will always be found those of



Pasteur, Koch, Pfeiffer, Ehrlich, Behring, Wassermann, Noguchi, and others.

Bacteria are divided into two classes, the good and the bad: saprophytic and pathogenic. The saprophytic bacteria are scavengers; they thrive best on dead tissues and assist in freeing the body of many waste products. Pathogenic bacteria thrive best on the living tissues of the host, in whom they are capable of producing disease. Their pathogenic action is due to the liberation of the toxins they contain or the elaboration of poisons in the tissues of the host.

Of these bacterial toxins there are two main types: The exotoxins, contained in bacteria whose poisonous principles are capable of being dissolved out of the bacterial cell. To this class belong the bacillus of diphtheria and the bacillus of tetanus. The great majority of bacteria, however, produce endotoxins, or poisons which are incapable of separation from the cell bodies by any of our known filtration methods. Examples of this are the bacillus of typhoid fever and the streptococcic and staphylococcic groups, etc.

While bacteria are capable of producing disease, it is not through their mere presence *per se*, for, as we know, our persons in health permit of the culturization of numerous pathogenic bacteria, therefore other factors must enter in, and these factors comprise the natural defensive mechanism of the body against disease.

*Natural Resistance.*—This varies greatly with the individual and has a certain selective action, for why is it that one person can harbor in his mouth virulent pneumococci and streptococci and yet can go through life without a single attack of pneumonia, and, conversely, be subject to repeated attacks of tonsillitis; whereas, another individual harboring the same organisms may have several attacks of pneumonia during his lifetime, and none of tonsillitis. This is due to the development of what we call *immunity*, which is the power of resistance the body tissues are able to exert against bacterial poisons. *Immunity* may be divided into species and racial immunity.

*Species Immunity.*—It is well known that many animals are naturally immune to diseases common to man, and that it is only with the greatest experimental difficulties that infections with those diseases can be made successfully.

*Racial Immunity.*—Also, among the different races of the same species there appears to be a natural immunity against certain

diseases, which have long been prevalent in that particular section, but which when carried to another section where fresh soil is obtained immediately light up into virulent epidemics. This is seen in the ravages of tuberculosis among the negroes and American Indians, and it is seen conversely in the immunity from yellow fever that has long been enjoyed by the negro.

*Acquired immunity* is the protection that is afforded an individual who has passed through an attack of one disease, this conferring a greater resistance to that disease in the future. This is commonly observed in diseases like typhoid and yellow fever. Acquired immunity may be either active or passive. "The process of conferring protection by treatment with either an attenuated form or a sublethal quantity of the infectious agent of a disease or its products is spoken of as active immunization," because the immunized individuals gain their power of resistance by taking an active physiological part in the acquisition of this new property of immunity. Thus active immunity can be acquired by repeated injections of attenuated cultures, as in Pasteur's work in hog cholera; by injections of sublethal doses of virulent bacteria, as demonstrated in the protozoön disease of Texas fever; by injections of killed bacteria, first suggested by Chauveau. This method of active immunization with gradually increasing doses of killed bacteria has been carried out successfully against many bacterial diseases. It is particularly useful against those groups of bacteria producing endotoxin; and, finally, by injections with bacterial products from poisons excreted or liberated from the bacterial cell body. These measures comprise *vaccination*.

*Passive immunity*, on the contrary, is that gained by the host through no active formation of antibodies on its own part, but rather accepting ready to hand the antibodies prepared by the tissues of another species. The most conspicuous types of this are the antidiphtheritic and antitetanic sera. These are both designed to meet bacterial exotoxins, and it is this type of sera that is most successful. On the contrary, antigonococcic, antistreptococcic sera, and the like, which depend for their activity on the lysin, opsonin, and other antibodies they contain, are not blessed with a like therapeutic success. Allen states that "these sera are not always curative; indeed, their use during active disease may not be altogether free from danger. Thus the administration of anticholera or anti-typhoid serum, which each depend for their activity on the lysin

they contain, may result in the extraleucocytic lysis of so many bacteria that the resultant flooding of the tissues with large quantities of their contained endotoxin may imperil the life of the recipient from the additional toxæmia."

Bacteria have a selective action: not only must they gain access to the body in large enough numbers and possessing sufficient virulence, but they must also gain entrance to a tissue that is suitable for their further development. For instance, you can rub a typhoid culture into an abraded surface of the arm or a culture of streptococci can be swallowed, both with equal impunity, but reversing the conditions a bacterial infection is sure to follow.

Now what are the general defences of the body against this bacterial invasion? They are fourfold:

1. *Antitoxin*, a substance manufactured by the tissues which is capable of neutralizing the soluble toxins produced by certain groups of bacteria.

2. *Agglutinin*, a substance which causes bacteria free in the tissues or blood stream to be clumped together in masses and held nearly immovable and therefore more accessible for phagocytosis. This is the more conspicuous where it concerns the motile bacteria. Though originally observed in 1889 by Charrin and Rogers, in studying the *Bacillus pyocyaneus*, the agglutination reaction is commonly associated with Widal, who first applied the phenomenon in the diagnosis of disease by an unknown organism.

3. *Lysin*, a substance or substances elaborated by the body which has the property of dissolving certain bacteria. Pfeiffer noted that guinea pigs which had been immunized against cholera bacilli could withstand the further intra-peritoneal injection of virulent cultures without harm, and found that the peritoneal fluids dissolved the organisms.

4. *Opsonin*, discovered and named by Wright, is a substance that prepares or sensitizes the bacteria for ingestion by the phagocytic elements of the white blood-corpuscles.

There are two types of bacterial infection: local and general. The former is best represented by boils; the latter is seen in diseases like typhoid fever, pneumonia, puerperal sepsis, and the like. When a person recovers from a bacterial disease like typhoid fever, it is by the body having gradually elaborated the foregoing antitoxins, agglutinins, lysins, and opsonins in amounts sufficient to cause the neutralization, destruction, and solution of the bacteria. The time

required in the manufacture of these substances varies in different diseases: 21 to 28 days, as a rule, in typhoid fever; 9 to 11 days, as a rule, in pneumonia, etc. So we have two biologic methods of treatment, serum and vaccine treatment, and the principle of the former is to supply these protective substances ready made (passive immunity) and in vaccination to stimulate the tissues to produce them more quickly, and, inasmuch as diseased tissues are more sluggish in locally manufacturing them, to utilize or exploit healthy tissues for the advantage of the enfeebled ones (active immunity). This, then, is the scientific basis for the action of vaccines. And now what are vaccines?

*Vaccines* are emulsions of the bodies of dead bacteria killed in various ways and suspended in suitable dosage in solution of normal saline.

There are two types of vaccines: heterogenous and autogenous. Heterogenous vaccines are prepared from infections similar to the case which is to be treated, but from infected material not derived from the patient himself. This type of vaccine may be, and usually is, polyvalent; that is, cultures are obtained from several infections of the same nature and therefore represent, possibly, several "strains" of the same organism. These heterogenous vaccines are commonly called "stock" vaccines, perhaps because they are prepared in quantities and held in readiness to be used in a given case on demand.

Autogenous vaccines are prepared from cultures grown from infected material obtained from the patient himself. In other words, they represent and are specifically the organism from the effects of which the patient is suffering and toward which you are assisting the patient to establish an immunity. Knowing these differences, it is not difficult to understand that biologists, bacteriologists, serologists, and clinicians of the thinking type are agreed that the autogenous group of vaccines fulfil best the scientific therapeutic requirements. Let me quote from an article recently published by a man whose authority is unquestioned: "With the exception of certain organisms, such as tubercle bacillus and the gonococcus, there is little reason for employing stock vaccines instead of autogenous, and there is abundant ground for believing that the use of stock vaccines will not only lead to carelessness of diagnosis and misinterpretation of the probable nature of the infection with consequent administration of the wrong species, but will sometimes be directly harmful.

"I am well aware that the argument has been advanced that laboratories are not sufficiently available to practitioners in all sections to make it possible for them to obtain autogenous vaccines, and would reply that in a measure this may sometimes be true; but the general demand for stock vaccines has been artificially stimulated by manufacturers, and the practical application of this method of treatment has outdistanced the scientific investigation of its merits. Instead of wholesome growth with the gradual provisions of local agencies where autogenous vaccines could be obtained, an unwholesome growth of this mode of treatment has been stimulated, and those who seek to keep up with the latest pronouncement of advertisement literature find themselves in a position of dependence upon stock vaccines in many cases. There can be no doubt that in some instances stock vaccines are satisfactory. Staphylococcus and typhoid and tuberculosis vaccine are instances, but the other forms, and especially streptococcus and pneumococcus and mixed vaccines, are of very doubtful efficacy.

"Here we come upon the field of variability in the organisms themselves, and, unless a growth has been prepared from the patient himself, the strain may be entirely different and inappropriate. It avails little to use mixed strains which require the reduction of dosage of the one possibly present and available strain below the point of usefulness because of the simultaneous injection of several other strains in the mixture which are of no use, or practically useless.

"As for stock mixture of heterogenous organisms designed for the treatment of cases in which no sort of accurate bacteriological diagnosis has been made, too vigorous condemnation cannot be phrased."

In my own personal experience I have met with many cases referred to me by other practitioners, cases on whom various stock vaccines had been tried for various lengths of time, in various dosages, with absolutely no improvement, and which have responded with surprising promptness to an autogenous vaccine, and have established an immunity that in many cases has lasted for years, and I personally have used in some cases stock vaccines of different types, giving them a thorough trial, only to become discouraged at their non-success, and have discarded them in given cases for autogenous vaccines with gratifying results.

On the other hand, I believe that stock vaccines of a single

or of a polyvalent single organism type have their place, and a very important place of usefulness, in the 48-96 hour interval that is often necessary to prepare the autogenous vaccine, after the bacterial identification in the specific case has been established, and I almost uniformly use this period to give one and sometimes two injections of the appropriate stock culture. Appropriate stock cultures may often be used with value in association with autogenous vaccines in selected cases.

A word or two now to ensure success in getting the proper bacterial results in culture taking. The first principle is to obtain your material free from contamination, and this requires the observance of special precautions according to the kind of material that is to be cultured.

*Urine:* Should always be obtained by sterile catheter, after the external meatus has been appropriately cleansed, and drawn off into a sterilized flask or bottle, to which no preservative should be added. It is better to catheterize the day specimen into one receptacle and the night urine into a separate one.

*Feces:* Should be obtained, urine-free, and specimens from first and last portion of the stool obtained and studied.

*Sputum:* Should be obtained with greatest care, because for practical purposes no mouth is germ-free, and alveolar pyorrhœa, infected tonsils, and the like are so common. Before retiring, the mouth should be carefully rinsed with sterile water and the teeth brushed with sterile toothbrush, and a closed vessel containing sterile water placed at the bedside. In the morning the mouth should again be rinsed thoroughly with the sterile water, gargled, and with the brush re-sterilized, by dipping in boiling water, the teeth should be thoroughly brushed and then a few mouthfuls of clean sterile water should be swallowed. After this the sputum should be expelled by coughing and caught in serial sterilized wide-mouth bottles (with sterile corks), and it is best that only one or two masses of sputum should be expelled into any one bottle and the bottles labelled and sent at once to the bacteriologist for immediate examination. The sputum should, after direct examination of stained specimens to determine morphologically the different types that may be present, be then "whipped" through several Petri dishes containing sterile water to further free the bacteria from surface contamination, and the final washed specimen planted upon the different culture media that will appear best suited for

their recovery in pure culture, as judged from the findings on the first direct examination.

Cultures taken from *boils*, or from *infected sinuses*, from *acne pustules*, from *tonsillar follicles*, and the like, should be made only after thorough appropriate cleansing and disinfection of surface relations, and then taken from a second or third portion of the material, discarding the first, by means of a platinum wire or a sterile capillary glass pipette inserted well within the cavity.

Cultures from *eye*, *ear*, or *nose* should have appropriate measures to secure success.

*Blood specimens* should always be obtained from a vein, preferably at the bend of the elbow, by means of an all-glass sterilized syringe of a capacity not less than 5 c.c. It is rarely necessary to cut down on a vein, but the arm should be thoroughly sterilized by tincture of green soap and water, by 5-10 per cent. lysol, by absolute alcohol, and finally by ether; personally I prefer not to use iodine. It is better to moderately tourniquet the upper arm before sterilizing the field in order to prevent thin-walled veins from collapsing under the pressure. The blood should be immediately plated and flaked in peptone and dextrosed broth.

*In Pulmonary Abscesses:* In suitable cases material may be obtained by lung puncture in the following way: After sterilizing the chest wall in the same manner as for blood cultures, the needle attached to an all-glass syringe, containing 3 c.c. of peptone broth, should be plunged into the lung at the proper point, as determined beforehand by clinical means, and 1 c.c. of the broth introduced and then reaspirated as far as possible and tubed. This measure will yield results in many cases properly selected clinically.

After getting suspected infected material, direct examination by means of variously-stained slide specimens should be made to determine morphologically and by staining reactions and relations whether one or more types of organisms are present, and, if the latter, how many and what types, and then, aided by this knowledge, proceed to utilize the various culture media that will best ensure recovery of each organism in pure culture. Here is where the thoroughly-trained bacteriologist will succeed and in the shortest time. It is often exceedingly difficult to recover a shyly-growing streptococcus or tubercle bacillus occurring in small numbers, let us say from a urine practically alive with the *Bacillus coli*. This may be accomplished by inhibiting or attenuating the growth of the

hardier, more freely growing organism by treating the culture medium in an appropriate manner, but unless this is accomplished it will be seen at once how useless it is to successfully treat a pyelitis of streptococcal or tubercular origin by using only the *B. coli* in the vaccine preparation. Hence the failure of many autogenous vaccines that are bacteriologically imperfect or incomplete.

In many cases of *chronic gleet*, however, the gonococcus is absent and the catarrhal inflammation kept alive by secondary invaders, which may then in combination serve for cure in absence of the primary invader.

After getting out every bacterial group contained in a given specimen, each in pure culture, these should then be studied with a view to their share in the production or continuation of the disease in question, and, guided by experience, clinical as well as bacteriological, a final judgment of the organisms concerned may be passed and the proper ones selected for use in the vaccine. They may all be combined in a single ampoule or may be placed singly or in pairs. Only the lower dosages, however, can be reached by making a mixed vaccine composed of many elements, on account of the combined dosage being too high to permit of safe injection.

We can now proceed to prepare the vaccine, in which the following steps are concerned:

1. To obtain an emulsion containing the bacteria in purity—an emulsion with a uniform suspension and as free from bacterial clumping as possible.
2. To standardize the emulsion—that is, to determine how many bacteria are contained in each cubic centimetre.
3. To kill the bacteria in the emulsion and then tube them—or
4. To decide upon the dosage of each ampoule or set of ampoules; to tube them still alive and then kill them.
5. To label, effectively, each ampoule and place them in sets of ten in compartment boxes or cartons, the lids of which are to be specifically marked with the names of the organisms they contain and in what dosage, and most particularly with directions for their use.

6. To be sure that all “controls” are sterile before allowing the vaccine set to leave the laboratory for use.

I shall not in this paper enter in detail into the technic required in the actual preparation of the vaccine, but I want to say a word



or two of caution to most carefully consider the best ways of killing the bacteria without impairing their immunizing properties. This can only be accomplished by a thorough knowledge of and observance of the thermal and chemical death-point of each group of organisms: a knowledge that will tell you which bacteria should be killed by heat and which by chemical measures, or by a combination of the two. If by heat, at what temperature and for how long sustained? If by chemical sterilization, by what chemical and in what strength? I have known many an autogenous vaccine—otherwise quite appropriately selected bacteriologically and otherwise faultlessly prepared—to be inert and to fail absolutely therapeutically for no other reason than that the thermal and chemical death-points were not carefully ascertained. And I doubt not that this applies equally to many stock vaccines.

Have we in vaccine therapy a means sufficient to combat all types of bacterial infections? I would answer emphatically "no," and I would add that harm may often come from their indiscriminate use and in the hands of the inexperienced and careless.

In epidemic meningitis, in typhoid fever, in pneumonia, in generalized bacteræmia, with or without ulcerative endocardial lesions, the use of vaccines for curative purposes has not been attended with great success, although occasionally a case is seen in which amelioration in severity of symptoms has taken place which rightly or wrongly has been ascribed to the use of the vaccine. I am by no means yet convinced that their use in such cases is unjustifiable, and believe that we may yet arrive by experience at some method of establishing proper dosages and proper intervals of injection for this class of acute fulminating infections that will produce better results.

The most suitable field for vaccines and the field in which the most brilliant results have been obtained lies in treatment of diseases, acute or chronic, that have a local focus of infection, such as furunculosis, carbuncles, abscesses, various bone infections, such as osteomyelitis, various skin infections, such as acne vulgaris, infected sinuses, pyelitis, empyema, various infections of the mouth, such as pyorrhœa alveolaris, infections of the nose and nasal passages and various post-gonorrhœal conditions, and various conditions of the respiratory tract.

And now a final word as to why vaccines fail in the hands of many workers, even in the above field of election—chiefly because

of insufficient knowledge governing the general laws of dosage and time intervals of injection; by selecting inappropriate points of injection; by disregarding the best time of day at which injection should be given, so that the patient isn't safeguarded during the "negative phase" period at which his antibody formation is at the lowest ebb, etc. For many of these points I would refer the student or interested worker to a close perusal of monographs on this subject, notably Allen on "Vaccine Therapy."

Finally, I would call attention to a common cause of failure in a neglect to realize that autogenous vaccines need to be frequently freshly renewed—*i.e.*, a new culture taken and a new vaccine prepared from cultures that represent more nearly the *status præsens* of the case; for it frequently happens that in long chronic conditions the bacteria, by mutation or other biological properties, become adapted more or less to the antibodies formed in the tissues of the host.

I was asked, before reading this paper before this body, whether I did not think it quite feasible and quite proper for druggists to establish autogenous and stock vaccine departments for the purpose of themselves making these products. I think I must already have answered this question to most of you. I do not think it is practical nor fitting that you should, nor do I believe that it would prove commercially a success. And let me close with the words of Sir Almroth Wright, one of the pioneers in this work, who states that for such skilled service as that demanded for vaccine therapy "is required a man who has spent years of study to master the technic; to know how to make the vaccines, to know where to look for the microbes, to know how to isolate them, and, most of all, a man with sufficient experience and ability to apply all these things."

1901 PINE STREET, PHILADELPHIA, PA.

## THE CHEMISTRY OF A CUP OF COFFEE.

From time to time numerous analyses of coffee have been made and published which, while giving some insight into the chemistry of the coffee berry, have not necessarily enlightened us as to the position of affairs in regard to the liquor obtained when coffee is prepared in the way commonly enjoined. The chemistry of the cup of coffee will obviously leave out of consideration the chemistry of

the "grounds." It is the infusion with which the following laboratory notes deal, and certain fresh indications, we believe, have been obtained which are worth presenting in view of their medical interest. The story is far from complete, but there are interesting incidents in it which, as far as it goes, are worth recording.

#### A COMPARISON BETWEEN COFFEE AND TEA.

From a pharmacological or, what should amount to the same, a dietetic standpoint tea or coffee ought in certain ways, at all events, to act similarly, since both contain the alkaloid caffeine which has a well-known and marked effect of stimulation upon the central nervous system. It is generally admitted, however, that the two beverages, though having one thing in common, afford different results. Tea, it is well to point out, contains a much larger proportion of the alkaloid than coffee, but in the preparation of tea in ordinary domestic practice a much smaller quantity of material is used than is the case with coffee. A common formula enjoined in the making of tea amounts to the preparation of 1.25 per cent. infusion of the leaf. Similarly, in the preparation of coffee the quantity of coffee usually directed to be used signifies a 6 per cent. decoction. Since tea contains from 3 to 4 per cent. of caffeine, and coffee seldom more than 1 per cent., it follows that as regards this alkaloid both infusions of coffee and tea made on common domestic lines will contain practically the same amount of caffeine volume for volume of fluid. The inference is that whether it be a cup of coffee or of tea, the dose of alkaloid will be the same. But according to the present investigation the caffeine in coffee infusion has quite different associates from those in tea. This would appear to be the case, inasmuch as while little caffeine is extracted from tea by cold water, we find that practically the whole of the caffeine in coffee is taken out. There seems to be little doubt, as we have shown in previous articles upon tea,<sup>1</sup> that the caffeine in tea is for the most part combined with tannin in the form of caffeine tannate, which is not very soluble in cold water, but is easily soluble in hot water. We think this is an important observation, for it points to the probability of caffeine existing in coffee in a quite different form which is

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<sup>1</sup>"The Chemistry, Physiology, and Æsthetics of a Cup of Tea," *The Lancet*, Jan. 7th, 1911, and Dec. 2nd, 1911.

easily soluble in cold water. Subsequent experiments showed that the caffeine in coffee is combined with a peculiar acid allied possibly to tannic acid, but exhibiting different properties from the tannin present in tea. Thus this acid (it has been called caffetannic acid by some observers) is not particularly astringent, has a sour coffee-like taste, does not coagulate gelatin, gives a light green colouration with perchloride of iron (whereas tannic acid of tea turns it black), does not make caffeine solutions thick as does tannic acid, does not precipitate alkaloids—*e.g.*, quinine—and, in fact, shows altogether different properties from the tannic acid of tea. It gives a precipitate, however, with lead acetate from which the acid can be separated by sulphuretted hydrogen. When coffee infusion is saturated with ammonium sulphate a precipitate is obtained which contains a small proportion of the total caffeine in the free state, whereas a tea infusion similarly treated gives an abundant precipitate containing nearly all of the caffeine, this precipitate according to our observations consisting chiefly of caffeine tannate.

#### THE ABSORPTION OF CAFFEINE MODIFIED BY ITS ASSOCIATES.

The caffeine tannate of tea is precipitated by weak acids, and the presumption is that it is precipitated by the gastric juice, and therefore the caffeine is probably not absorbed until it reaches the alkaline alimentary tract. In the case of coffee, however, in whatever form the caffeine may be present, it is soluble in both alkaline and acid fluids, and therefore the absorption of the alkaloid probably takes place in the stomach. This fact may have an important physiological significance when we consider the comparative stimulating effects of the two beverages. If our view is correct coffee should act more promptly than tea as a stimulant and restorative, looking to its physiological action as due for the most part to caffeine. In practice it is generally accepted that coffee is a more powerful restorative than tea. The use of strong coffee as an antidote in poisoning by narcotics, notably morphia, is of interest in this connexion. Tea is mentioned for the same purpose, but only rarely. Apart from the consideration that caffeine has probably a more rapid action when taken in the form of coffee than in the form of tea, because the caffeine in coffee is more readily absorbed, it must also be remembered that coffee is often made with a generous proportion of the powdered bean, as in the case of the after-dinner "black" coffee,

the view being that the secret of good coffee is to make it strong. This, of course, is an entirely æsthetic demand, which may likely enough be opposed to physiological morality.

#### THE STRENGTH OF COLD WATER EXTRACTS OF COFFEE COMPARED WITH BOILING WATER EXTRACTS.

The fact that the caffeine in coffee is completely soluble in cold water suggested making a comparison as to the composition of the cold and hot water infusions in regard to other constituents. For this purpose several types of coffee were chosen, all of which reached this country through Costa Rica. As will be seen from the accompanying table, the varieties examined were as follows: Raw (*i.e.*, unroasted) Costa Rica, common quality; raw Costa Rica, finest quality; pale roasted Costa Rica, common quality; pale roasted Costa Rica, finest quality; high roasted Costa Rica, common quality; and high roasted Costa Rica, finest quality. The results are instructive, and we may proceed to consider the differences in composition of the infusions, both cold and hot, shown where raw, pale roasted, and high roasted coffee are employed, and the relationships, if any, of these differences to the discrimination supplied by the expert taster, who describes a particular coffee as, in his own words, "common" or "finest."

It is a somewhat remarkable fact that cold water extracts from coffee the same weight of materials as boiling water, but it must be admitted that the former infusion is somewhat less palatable than the latter. Chemically, however, there is little difference between them, and we may presume that physiologically a cold water extract of coffee will be much the same as a hot water infusion, leaving out æsthetic considerations, although these, of course, are exceedingly important, from all dietetic aspects. It is probable that cold water fails to extract certain oily bodies or fats which contribute attractive taste and aroma. The total extract is frequently higher in cold than in hot water. And not only is caffeine extracted from coffee equally well by cold and hot water, but this is true of the mineral salts and of the peculiar acid known as caffetannic acid, the acid which corresponds to the tannin of tea. In regard to the proportion of materials soluble in cold water coffee shows an entirely different result to tea, inasmuch as while coffee yields about 25 per cent. of its weight to cold water (an amount which is not increased

when hot water is used) tea yields only 12 per cent. of its weight to cold water, which is increased to 25 per cent. when the infusion is made with hot water. Again, cold water extracts from tea only 17.5 per cent. of its total caffeine, while from coffee it extracts the whole. Similarly, cold water extracts from tea 13 per cent. of its total tannin, while coffee under the same treatment yields practically the whole of its caffetannic acid.

### THE EFFECT OF ROASTING.

An infusion of green or unroasted coffee is singularly nasty to the palate, and it follows that the roasting process renders coffee the palatable article that it is. The chemistry of roasting amounts largely to a caramelisation process, during which certain oils and aromatic principles are formed as products of a mild destructive distillation. Curiously enough, there is little loss of caffeine in this process, as our results show, which is remarkable in view of the fact that caffeine sublimes at high temperatures. There are two degrees of roasting adopted—viz., pale roasting and high roasting. The important chemical effect of roasting, according to our analyses, is to diminish considerably the amount of caffetannic acid. If the figures in the table be consulted it will be seen that while in an

#### *The Analysis of Hot and Cold Infusions of Coffee.*

Constituent.	Raw Costa Rica (common).		Raw Costa Rica (finest).		Pale roasted Costa Rica (common).	
	Hot infusion.	Cold infusion.	Hot infusion.	Cold infusion.	Hot infusion.	Cold infusion.
Total extract.....	29.16	30.83	29.60	31.50	25.33	24.00
Ash of extract.....	4.16	3.88	4.00	3.88	4.16	5.66
Caffetannic acid.....	9.60	8.63	9.66	7.83	6.10	5.80
Total caffeine .....	1.00	1.33	1.21	1.56	1.11	1.11

Constituent.	Pale roasted Costa Rica (finest).		High roasted Costa Rica (common).		High roasted Costa Rica (finest).	
	Hot infusion.	Cold infusion.	Hot infusion.	Cold infusion.	Hot infusion.	Cold infusion.
Total extract.....	23.50	25.66	24.30	24.00	25.60	23.00
Ash of extract.....	3.50	4.50	4.66	4.00	4.00	4.50
Caffetannic acid.....	6.60	5.90	3.90	3.16	3.63	3.87
Total caffeine .....	1.05	1.06	1.23	1.11	1.05	1.20

infusion of raw coffee (unroasted) the caffetannic acid amounts to 9.60 per cent., it is in the pale roasted 6.60 per cent., while by further roasting, as in the "high roasted," it is reduced in the infusion from 3.63 to 3.90 per cent. What part caffetannic acid exactly plays as a dietetic constituent of coffee it is difficult to say, but if it should prove to be an undesirable element, then the high roasted coffees are least open to objection on this account. It may be noticed also that the raw coffee yields a greater percentage of soluble constituents to both cold and hot water than high roasted coffee, the pale roasted coffee showing intermediate results. Roasting, amongst other things, has, therefore, the effect probably of rendering certain bodies insoluble—*e.g.*, albumins—while the slight burning effect upon carbohydrates would produce possibly some free and of course insoluble carbon.

#### QUALITY OF COFFEE IN RELATION TO CHEMICAL COMPOSITION.

From the results recorded in the table it will be seen that no definite relation can be traced between the æsthetic quality of coffees, classed respectively as "common" and "finest," and the chemical composition of the infusions which they yield. It may be noted that there is no important difference in the amount of the drug caffeine when the common and finest varieties are examined. It is probable that the æsthetic values—flavour, body, aroma, and so forth—are related in some way to the amounts of oil bases or aromatic principles present, and these are in any case minute. Whether they are present in appreciable quantity or not doubtless depends upon the care spent upon the roasting process. At any rate, it is conceivable that a point in the roasting process could be reached which would deprive the coffee of all attractive flavour, while it is certain that the infusion of the raw unroasted berry is not fit to drink on account of its unpleasant taste. Recently it has been announced on more than one occasion that pyridin is an important constituent of coffee. We have certainly found it present, but not in sufficient quantities to estimate. It is rather a curious fact that some authorities mention that coffee often relieves asthma, while pyridin is described as "useful in the treatment of asthma" and "beneficial in cardiac dyspnœa, emphysema, and angina pectoris," and, finally, that "it is probably the relieving agent of various cigarettes and powders smoked or burnt for asthma and whooping-cough." Another constituent of coffee

produced by roasting is caffeol, a nitrogen-containing oil, but it would be impossible to differentiate the quality of coffee upon an analysis pursued in this direction, inasmuch as the amount found does not exceed more than 0.06 per cent. It is doubtful whether it has any further value from a dietetic point of view than that supplied by its influence in pleasing the senses. When isolating caffeine from coffee infusion the solvent (chloroform) takes out also a non-crystalline substance which unlike caffeine is soluble in ether. This substance has a very strong, pleasant, but somewhat bitter flavour of coffee. The yield is different according to the quality of the coffee examined, and it is possible that this principle is a determining factor in the judgment given by the expert coffee taster. It is a product of roasting and does not exist in raw coffee.

#### FOOD VALUE OF COFFEE.

The infusion of coffee presents practically very little material that is of direct nourishing value, but by diminishing nervous fatigue, by virtue chiefly of the caffeine present, it may increase muscular power. It is not itself a builder of tissue. The use of coffee after dinner, it is of interest to note, is justified in a large number of cases by the fact of its stimulating effect upon the vital centres, and it is said to serve to some extent as an antidote to alcohol. It is commonly claimed to remove drowsiness; as a matter of fact, in many subjects it produces drowsiness, but this is usually followed quickly by marked wakefulness. The practice of drinking coffee after a meal for the sake of the stimulus which is experienced has much to be said in its favour dietetically. There is no reason for supposing that coffee possesses any value as a food. The berry contains a quite important proportion of fatty substances (12 per cent. average), but these are necessarily excluded from the infusion, as owing to their insolubility they remain in the "grounds."

According to our analyses again the protein contents of a cup of coffee are small, approximating to 1.25 per cent. of the coffee extracted. This amount can have little dietetic significance. There is also a trifling quantity of dextrin and sugar present besides traces of alcohol, which again can possess no importance from a physiological point of view.—*The Lancet*, Nov. 29, 1913, pp. 1563-1565.



## BOOK REVIEWS.

PHARMACEUTICAL BOTANY. By Heber W. Youngken, Assistant Professor of Botany and Pharmacognosy at the Medico-Chirurgical College, Philadelphia. P. Blakiston's Son & Co., Philadelphia.

To speak of this little book of less than a hundred pages as a dictionary or a glossary is not to belittle its value to the student. The illustrations, as, for example, those on stem and leaf structure, are especially well chosen, and their pictorial value is worth many words of text, which, of course, is not a factor of this book. From almost any aspect of thought the book seems like a list of terms, but these terms are well arranged and with a good regard to system. The desire to make the definitions brief has made them in many cases almost meaningless except just as a reminder to one who already knows what the term means.

As a whole, the acknowledged desire of the author has been well attained, but there is a question whether such an object is especially advisable. A student is apt to be just as human as the average person with a consequent eagerness to have before him a volume which is "readable" even though it is for purposes of study. The feeling arises in us, as we look over the volume in hand, that it is a mighty nice little book to turn to once in a while, but that it would rather strain our devotion to science if we were called upon to use it as a text-book from which to gain our first insight into a new subject.

A. K. LOBECK.

ANNUAL REPRINT OF THE REPORTS OF THE COUNCIL ON PHARMACY AND CHEMISTRY OF THE AMERICAN MEDICAL ASSOCIATION for 1913, with the Comments that have appeared in the JOURNAL.

"The more strictly scientific parts of the reports, both from lack of space and because of their technical nature, have been abstracted or entirely omitted from the reports as published in the JOURNAL. Believing that these scientific investigations should be available to scientists in general, especially to chemists, pharmacologists, and others interested in medicine, the Council has authorized the preparation of this volume, containing the complete reports of the Council adopted prior to January 1, 1914, as well as the comments which have appeared at the time of publication."

These reports are a valuable addition to the literature that has

accumulated in the last few years on proprietary remedies and nostrums.

Previous to the last decade investigative work of this sort in reference to remedies of this kind was hardly thought of, although there may have been dreamers who had hopes and visions of what the future might bring forth. We do not use the word "dreamers" in any offensive sense. Dreamers with initiative and honesty of purpose are the compelling force in this world, and it is gratifying to know that there are men of this type in medicine and pharmacy who are willing to work disinterestedly for the body politic.

Pharmacists who desire to add to their efficiency and usefulness would do well to add these reports, which have been appearing for several years, to their library.

JOHN K. THUM.

NEW AND NONOFFICIAL REMEDIES, 1914: Containing Descriptions of the articles which have been Accepted by the Council on Pharmacy and Chemistry of the American Medical Association Prior to January 1, 1914.

This work epitomizes one phase of the revolution that has taken place in medicine the last decade. It typifies the passing from darkness into the light of reason of things pharmacological, or rather the exploitation of modern materia medica. Indeed, it fills a long-felt want in both the profession of medicine and pharmacy. When one stops to consider the inaccessibility of information relating to unofficial remedies previous to its publication it hardly seems possible that we ever got along without it.

Essential information relating to biological remedies such as serums, vaccines, and tuberculin preparations is given in a manner convenient to the seeker after such knowledge.

JOHN K. THUM.

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## CURRENT LITERATURE.

UNIFORMITY IN DRUG STANDARDS.—In a contribution to the *Journal of the Kansas State Medical Society*, entitled "A Plea for Uniformity in Drug Standards and for Uniform Requirements in Dispensing," L. E. Sayre makes some interesting observations: "If what is prohibited within a state is permitted beyond its borders,

the statutes of prohibition become not only inefficient, but most useless. If what is prohibited within a drug store is permitted in a physician's dispensary, the law likewise becomes measurably inoperative as far as the public is concerned."

He makes the statement that such conditions exist and that in some of the different states the evil has been exposed. He quotes Mr. Roemer, who, at a meeting of the New York Pharmaceutical Association, made the announcement that an investigation of some of the medicines dispensed by physicians showed a sad state of affairs; heroin tablets containing no heroin, morphine tablets without morphine, and elixir of terpin hydrate in which the terpin hydrate was conspicuous by its absence!

Mr. Sayre believes that the interest of the public could be safeguarded by the state laws requiring all medicine dispensed by physicians to *bona fide* patients to conform to legal standards, and, further, that any place where drugs are compounded, dispensed, or sold should be amenable to official inspection.

If dispensing by medical men has resulted in conditions which are prejudicial to the public health—and from this standpoint alone should the question be viewed—then legislative regulation must, and no doubt will, be undertaken by the various states. This question is beginning to loom up as never before and must be settled sooner or later. It probably would be a good plan if the various state medical and pharmaceutical societies at their coming meetings for the year were to take hold and thresh this matter thoroughly and formulate some definite opinion upon the whole subject.

JOHN K. THUM.

CHEMICAL EXAMINATION OF *DICOMA ANOMALA*. By Frank Tutin and William J. S. Naunton. The Wellcome Chemical Research Laboratories, London.

The material employed for this investigation consisted of the entire air-dried plant of *Dicoma anomala*, Soud., obtained from South Africa.

An alcoholic extract of the plant, distilled in a current of steam, yielded a small amount of an essential oil. The portion of the extract which was soluble in water yielded a small amount of a colorless crystalline glucoside, and a large amount of a yellow amorphous product, which, on hydrolysis with alkali, gave 3:4-dihydroxycin-

amic acid. The aqueous liquid contained, furthermore, a quantity of sugar which yielded d-phenylglucosazone, melting at  $218^{\circ}$ .

The portion of the extract, which was insoluble in water, formed a dark-colored, resinous mass. It consisted largely of amorphous products, some of which gave 3:4-dihydroxycinnamic acid on hydrolysis, and a small amount of an amorphous alkaloid was also present. The following definite substances were obtained from the resin: Hentriacontane  $C_{31}H_{64}$ ; a phytosterol  $C_{28}H_{46}O$ ; palmitic, stearic, arachidic, cerotic, and melissic acids, together with some unsaturated acids which appeared to consist chiefly of a compound,  $C_{16}H_{30}O_2$ , such as has been obtained by Bull (*Ber.*, 1906, 39, 3537) from cod-liver oil.

J. K. T.

## PHILADELPHIA COLLEGE OF PHARMACY.

### ANNUAL MEETING.

The annual meeting of the Philadelphia College of Pharmacy was held March 30th, at 4 P.M., in the Library; the President, Howard B. French, presiding. Twenty-two members were present. The minutes of the quarterly meeting held December 29th, 1913, were read and approved. The minutes of the Board of Trustees for December 2nd, 1913, January 6th, February 3rd and 9th were read by the Registrar, J. S. Beetem, and approved.

President French delivered his Annual Address, when Mr. Berlinger moved that the address be referred to the Publication Committee, as there were many items of information that should be given to the public through THE AMERICAN JOURNAL OF PHARMACY, particularly the items referring to the instruction as given in the College. Seconded, and so ordered. (See p. 233 in this issue of this JOURNAL.)

REPORT OF THE PUBLICATION COMMITTEE was read by Professor S. P. Sadtler. The JOURNAL has been published regularly during the past twelve months. The financial statement presented shows a creditable balance after paying all bills. It is impossible to supply a complete set, as some of the earlier volumes have one or more numbers missing. It is hoped that the sale of back numbers will increase so that a general index since 1890 can be published. There is need for such an index, as is shown by a number of inquiries for

one, and even orders have been received. In discussing the report Mr. Beringer asked if it was possible to reprint the missing back numbers in order to supply complete sets. Professor Remington suggested making use of a photographic process, in place of printing, to replace back numbers, when Mr. England moved that in order to secure reprints of back numbers the subject be referred to the Publication Committee, with power to act. So ordered.

REPORT OF COMMITTEE ON PHARMACEUTICAL MEETINGS.—Professor Kraemer said that the work done during the past few years has not been all it should be, owing to the fact that (as there are so many pharmaceutical societies in Philadelphia) there was a corresponding division of energy. Yet there are some indications that our College may be able to come back to the work in the old spirit and with renewed vigor. In addition to the meeting last May, when the students of the graduating class presented abstracts of their theses, there have been three other meetings held. The first of these was in October, when Professor Eugene Charabot, of Paris, gave a charming address in French on "The Formation and Distribution of Odorous Products in Plants." This was rather a unique occasion in that a large number of students were present and nearly every one expressed delight in the privilege of hearing this discourse. The article was printed in full in the JOURNAL, translation having been made. He also stated that he had just received a request from the editor of a Hungarian periodical to reprint the address.

Another meeting was held in November. Professor La Wall had an article on the "Detection of Chicory in Decoctions of Chicory and Coffee." This paper caused a great deal of interest, and was published in full in the JOURNAL. Mr. Boring exhibited several specimens of elixir of iron, quinine, and strychnine, and Professor Remington gave an illustrated lecture on "Some Pharmaceutical Celebrities I Have Met"; also touching on the pharmaceutical colleges and the professional aspect of pharmacy in Europe, especially England and Germany.

The third meeting was held in February, when Mr. Lobeck gave a talk on "A Roughing Trip Across the Continent," illustrated with colored photographs. It was a very practical talk not only on how one should arrange a vacation, but to get the most out of it.

EDITOR'S REPORT, read by Professor Kraemer. During the past year we have published 572 pages, exclusive of a 10-page index. This matter included 75 original and selected papers covering a wide

range of subjects relating to pharmacy. We have received the support of investigators in various parts of the United States and those connected with other colleges; our own members continue to contribute articles and in other ways promote the objects of the JOURNAL. The following graduates have contributed articles during the year: George M. Beringer, George M. Beringer, Jr., Dr. Robert A. Hatcher, Victor O. Homerberg, Henry Kraemer, Professor Charles H. La Wall, Dr. Frederick B. Power, Sister Bertha Müller, Professor Joseph P. Remington, John R. Rippetoe, John K. Thum and M. I. Wilbert, and from the Honorary Members: Professor Charles E. Bessey, Professor W. G. Farlow, Professor A. Tschirch and Dr. A. L. Winton.

The Quarterly Report on Progress in Pharmacy, by M. I. Wilbert, continues to be one of the important features of the JOURNAL, as it gives an excellent *résumé* of discoveries of interest to medicine and important happenings in pharmacy. During the past year we have published a number of general articles which have given in a nutshell some of the advances in modern science. Among these articles we mention Ehrlich's Chemical Therapy, Phylacogens, Colloids and Crystals, Enzymes, and Phenomenon of Catalysis.

CURATOR'S REPORT, read by J. W. England. The Museum of the College is growing yearly in importance. The entire collection of drugs and drug products and the Martindale Herbarium should be relabelled. The containers for the drugs should be standardized to two sizes only. The Museum could be made more valuable to the pharmaceutical public as a place of reference for standard or typical drugs and drug products, and most interesting also to the general public, if the historical collections were properly displayed. The Museum consists in large part of typical specimens of rare drugs. It should be improved by the addition of typical specimens of the more commonly used drugs as well, and especially by a proper display of our historical matter and apparatus.

The recommendations and suggestions in the Curator's report were, on motion, referred to the Board of Trustees.

LIBRARIAN'S REPORT, read by Professor Sadtler. During the year the Library has added by purchase, gifts, and exchanges a total of 105 volumes, 80 volumes of periodicals and theses have been bound, 2384 books have been accessioned, classified, and shelf-listed, making a total of 7264 books ready to be catalogued. Use

of Library during the year by 1375 persons, an increase of 378 over last year.

The report of the Committee on Nominations was read and ordered, entered and filed.

A communication was read from C. Carroll Meyer, declining the nomination for membership in the Board of Trustees because of pressure of business preventing his attendance at the meetings.

The President appointed Professor F. X. Moerk, Mitchell Bernstein and E. H. Hessler tellers, to conduct the election. The report of the Committee on Nominations being again read, the members proceeded to a ballot. While the ballots were being counted, Professor Stroup alluded to a recent notice received from the Fire Marshal and quoting an Act of Assembly prohibiting smoking in any part of the building. He hoped there would be some modification of the rule so as to permit smoking in the corridor, which was entirely fireproof. Past experience had shown that when prohibition was enforced the entrance and the street in front of the College were used as a place for smoking and a number of complaints and police troubles had resulted. A number of the members related various experiences, viz., President French, Professors Remington, Kraemer, Sadtler, Lowe, Messrs. Beringer and Poley; the speakers generally thinking that, while protection from the risks of fire was absolutely necessary, some means should be devised to permit smoking in some part of the building. The discussion was closed by President French stating he would confer with Director Porter regarding the matter.

The tellers reported the results of the election as follows:

President, Howard B. French; first vice-president, R. V. Mattison, M.D.; second vice-president, J. L. Lemberger; treasurer, Richard M. Shoemaker; corresponding secretary, A. W. Miller, M.D.; recording secretary, C. A. Weidemann, M.D.; curator, Joseph W. England; editor, Henry Kraemer; librarian, Katharine E. Nagle; trustees for three years: Joseph P. Remington, C. Stanley French, George B. Evans; Publication Committee: Samuel P. Sadtler, Henry Kraemer, Joseph P. Remington, Joseph W. England, Martin I. Wilbert, Charles H. La Wall, and John K. Thum; Committee on Pharmaceutical Meetings: Henry Kraemer, Joseph P. Remington, C. B. Lowe, George B. Weidemann, and E. H. Hessler.

The President declared the above duly elected.

The President made the following appointments:

Committee on By-Laws: George M. Beringer, Joseph W. England, and C. A. Weidemann.

Delegates to the Pennsylvania Pharmaceutical Association: C. B. Lowe, Joseph P. Remington, F. P. Stroup, O. W. Osterlund, William E. Lee, Charles H. La Wall, and E. Fullerton Cook.

Delegates to New Jersey Pharmaceutical Association: Henry Kraemer, George M. Beringer, C. B. Lowe, Charles H. La Wall, and H. P. Thorn.

Delegates to Delaware Pharmaceutical Association: A. W. Miller, M.D., C. B. Lowe, and H. J. Watson.

The President announced the death of David H. Ross on January 26, 1914. He joined the College in 1888.

William M. Morrison presented an old scale and two cases of instruments originally owned by Dr. Stott, who died in 1837. The thanks of the College were tendered the donor.

C. A. WEIDEMANN, M.D.,  
*Recording Secretary.*

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## ABSTRACTS FROM THE MINUTES OF THE BOARD OF TRUSTEES.

*December 2, 1913.*—Sixteen members present.

Committee on Library reported total number of books accessioned to date 5449. A number of books were purchased during the month and the Library was used by 154 persons.

A communication from the Board of Public Education was read, recommending that Miss Florence McGarrity be awarded a scholarship; and, on motion, the recommendation was approved.

An application for active membership was received from a graduate of the 1913 class, now a resident of China, and, as usual, it was referred to the Committee on Membership.

The Treasurer reported that on November 8th Mrs. Anna Shinn Maier sent her check for \$2000 to establish a scholarship in memory of her father, James T. Shinn, the income from said amount to be devoted for scholarship purposes. On motion, it was voted that the Treasurer convey the thanks of the College to Mrs. Maier.

*January 6, 1914.*—Fifteen members present.

Committee on Property reported the change from white to green



shades in the electric light over the lecture table in the Materia Medica room.

A petition signed by 75 per cent. of the students relative to the establishment of a lunch room in the College building was submitted by the Property Committee. The Dean explained in detail the reasons that prompted the presenting of the petition by the students, and advocated the adoption of a plan complying with their request. After some discussion it was moved that the Board approve the plan if the Committee on Property found that same could be put in operation without the College being compelled to assume any responsibility. It was so ordered.

Committee on Library reported 476 books accessioned and shelf-listed during the month. A number of books had been donated and 190 persons had used the Library during the month.

Committee on Accounts and Audit reported they had examined the accounts of the Treasurer, Registrar, and the AMERICAN JOURNAL OF PHARMACY, and found them correct.

Committee on Announcement reported the publication of the December issue of the Bulletin, that Pharmacy Talk No. 1 had been sent out, and that they had in preparation a series of 8 "Talks"—one to be issued each month.

The Corresponding Secretary of the College read several letters from those who were recently elected to Honorary Membership in the College.

The Committee on Membership having reported favorably on the application of Mr. Job Fong, of Canton, China, for active membership, a ballot was taken and he was unanimously elected.

*February 3, 1914.*—Fourteen members present.

Committee on Property reported that inquiries had been made and it was found to be possible to make arrangements with a caterer to serve a light lunch in the College building for the accommodation of the students. On motion, the matter was referred to the Committee on Property with power to act.

Committee on Library reported that 454 books were accessioned during the month, making a total of 6378 books ready to be catalogued. The Library was consulted by 143 persons.

Committee on Instruction reported progress concerning matters that they had had under consideration.

The Chair announced that Dr. P. S. Stout had been requested to present a report of the Alumni Special Committee having in

charge the Centennial Fund, and asked that the regular order of business be suspended. This being agreed to, Dr. Stout was introduced and presented a detailed report of what had been done up to this time. The main object of the movement is to obtain by subscription and bequest, as may be most acceptable to the donor, a fund of \$500,000 or more, to be devoted to improvements—location, building, equipment, etc., and to the establishment of an endowment for the College. The action of the committee was endorsed, and the Board gave assurance of furthering the movement in every way possible.

Committee on Examinations reported they had been engaged for several months in formulating a set of rules for regulating the conduct of examinations in the College. A number of recommendations were submitted and extended discussion followed. As this was an important matter, it was voted that further consideration of the subject be deferred to an adjourned meeting to be held February 9th.

The Dean presented the form of certificate which the Board had some months before referred to a Special Committee for consideration, covering special branches of study. The form met with approval, and it was voted that certificates be finished in accordance with the outlines proposed.

An application for active membership was received and referred to the appropriate committee.

*February 9, 1914.*—Eleven members present.

This meeting was called to give further consideration to the report of the Committee on Examinations. After an extended discussion, participated in by many of the members, action was deferred.

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## PRESIDENT'S ADDRESS.<sup>1</sup>

*To the Members of the Philadelphia College of Pharmacy:*

Your President has pleasure in submitting at this time, in accordance with his established practice, a brief summary of matters of general interest relating to your institution.

The College buildings at the present time are in good condition. The walls and ceiling of the library have been painted, the floor covered with a cork carpet, and new chairs provided. The walls of the back stairway have been coated with a light-colored paint, which has proven of advantage in brightening up this portion of

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<sup>1</sup> In abstract.

the building. Alterations were made in the third-floor Microscopical Laboratory, giving greater facilities for the revised and expanded course in Bacteriology, which is now an obligatory course in charge of Prof. John A. Roddy. Changes have also been made in Alumni Hall for the benefit of the classes in Microscopy.

Following the approval of the Board of Trustees of a petition signed by a number of the students, asking that a lunch-room be established, a lunch counter was started a few weeks ago and is being continued with increasing success. The lunches furnished are substantial and wholesome, and from the patronage received it would appear that the students in general appreciate the innovation. The Property Committee will, no doubt, find it necessary, in the near future, to enlarge the facilities for this purpose, as the present accommodations are not equal to the demand.

The total number of students in attendance at the College at this time is 434, an increase of fourteen over last year. Of the number mentioned, 145 are first-year students, 109 second-year students, 141 third-year students, 38 special chemistry students, and 1 student taking the Food and Drug course. There were 168 first-year matriculants—167 regulars and 1 special. Of this number, 1 student is deceased and 22 are not attending. The second-year matriculants numbered 113—112 regulars and 1 special. Of this number, 4 are not attending. There were 124 regular third-year matriculants and 18 students remaining from class of 1912-13. Of the total of 142 third-year students, 1 is not attending.

Of those seeking admittance to the College at the beginning of the fall term, 29 applicants were not able to furnish satisfactory entrance credentials. These were given the privilege of remaining at the College and repeating the first-year work during 1914-15, in the meantime being expected to qualify. A few of the number have availed themselves of this privilege, but of these only four are attending at the present time, and under the circumstances are not listed as students.

In the department of Analytical Chemistry, 13 first-year, 28 second-year, and 35 third-year students have been doing special work. Of the number of third-year students mentioned, 9 are doing thesis work. Twenty-five students are taking the special laboratory course in Bacteriology; of this number, 7 are specials and 18 regulars. Fourteen of the special Chemistry students are availing themselves of the special course in Microscopy; and 10

students are doing special work in the Microscopical Laboratory, in connection with their theses.

The work in the Department of Pharmacy for the course of 1914-1915 is being successfully carried on.

The recording of the attendance, as now required by the State Pharmaceutical Board, has been of considerable value, and resulted in a higher grade of scholarship being attained by the classes.

The extra lectures on pharmaceutical subjects given during the college courses have been of material value and more largely attended.

The course in Commercial Training, under the control of the Department of Pharmacy, and for which the students are not charged, has been greatly increased; the number of hours devoted to this branch has been doubled since last year. Illustrative material is fully shown, bookkeeping methods are compulsory, and students are now required to keep an individual set of books and submit them for examination.

The Department of Botany and Pharmacognosy has given evidence of considerable advancement during the past year. A specialized course in Microscopy has been developed, giving the special chemistry students enlarged opportunities for increasing their efficiency and broadening their powers as analysts. The course comprises a series of laboratory periods on Saturday mornings and includes a wide range of topics, namely, the study of drugs, foods, and technical products with their deterioration and adulteration. The large number of specimens bearing upon this work, which your Professor of Botany and Pharmacognosy and his assistants have been diligently collecting for a number of years, is now being brought into practical use, and is proving of great advantage.

It is of interest to note the increasing demand among agricultural experiment stations and the government laboratories for pharmacognocists or thoroughly trained analysts; and as microscopical courses are not, as a rule, included with chemical courses given in this country, the Philadelphia College of Pharmacy, in the establishment of such a course, will undoubtedly be enabled to prepare students of chemistry for a broader knowledge and a deeper understanding of the intricacies of the work they have elected, thus extending the educational prestige of the College.

The greenhouse and roof garden continue to furnish the students in Botany and Pharmacognosy facilities for growing plants and conducting special investigations.

In the Department of Materia Medica the Physiological assay of drugs has been given increased attention, with good results. Your Medical Examiner reports that the physical examination of your students is somewhat hampered by lack of sufficient light. It may, therefore, be necessary for your Committee on Property to install a special light for this purpose in the near future.

On Thursday evening, May 22, 1913, the 92nd Annual Commencement exercises of your College were held in the Academy of Music. The graduating class numbered 123, representing 22 States of the Union, District of Columbia, Canada, China, and Russia.

During the past year the College has received from Mrs. Anna Shinn Maier, daughter of your late treasurer, James T. Shinn, a sum sufficient to convert the Shinn Memorial into a scholarship.

The Pennsylvania Scholarship Fund of \$2500 is nearing completion; \$2200 has been collected.

There are at present 148 active members of your College, and 13 associate members. During the year 6 active members and 1 associate member were elected. The resignation of one active member was received; and your President regrets to report the death of three of your active members during the year, as follows:

John W. Ridpath, May 8, 1913. Joined the College in 1888.

Evan T. Ellis, September 29, 1913. Joined the College in 1852.

David H. Ross, January 26, 1914. Joined the College in 1879.

It is of interest to note that Evan T. Ellis was the oldest member of the College.

It is thought desirable by your President to bring to your attention the fact that the Department of Public Safety of Philadelphia, recognizing the danger incident to smoking in buildings where people are assembled in numbers on various floors, deemed it necessary to send a communication to your College, reading as follows:

MR. HOWARD B. FRENCH, *President*,  
Philadelphia College of Pharmacy,  
145 No. 10th Street,  
Philadelphia.

DEAR SIR:

Complaint has been made to this Bureau of the promiscuous smoking of cigarettes and cigars in the building of the College of Pharmacy.

The Fire Marshal has made an inspection of the complaint and considers it of vital importance that the practice be discontinued at once.

I therefore request that proper notices be placed in all parts of the building where there are no tile or cement floors, in order that those offending may have knowledge of the fact that it is in violation of the Act of Assembly.

I would appreciate it if you would give this the publicity it deserves.

Yours very truly,

(Signed) GEO. D. PORTER,  
*Director.*

The body of this communication has been printed and prominently displayed throughout your buildings; and it is earnestly hoped that students in the College will respect said notice by discontinuing the practice of smoking in the portions of the buildings where there are no tile or cement floors, and that arbitrary measures to enforce the order may not be found necessary.

Your President wishes to call attention to the fact that on the 21st of March, 1921, the College will have attained the one hundredth anniversary of its existence. This is but seven years away, and your President desires to urge upon all members of the College the desirability of collecting and placing in possession of the College any historical matters they may have or may be able to obtain. He would suggest that old prescription labels and labels referring to specific preparations could be readily collected from time to time from many of the old drug stores, and would prove of much interest. He also hopes that a strenuous effort may be made to collect as many of the old-time appliances as possible. It is the earnest hope of your President that when celebrating the 100th birthday of the College there may be an historical exhibition at that time that will not only attract the attention and interest of the pharmacists throughout the country, but of members of the medical and allied professions.

In closing, your President desires to express appreciation to those of the officers and faculty who have so heartily coöperated with him during the past year; and to those who have not been in full accord with his views, he wishes to express the hope that all personal feelings may be put aside and that a united effort may be made to continue the prosperity and advancement of this institution, which is dear to the hearts of all those associated with it.

HOWARD B. FRENCH.

March 30, 1914.

## THE VITAMINES.<sup>1</sup>

### THE RECOGNITION OF ESSENTIAL CONSTITUENTS OF THE DIET HITHERTO UNCLASSIFIED—DEFICIENCY DISEASES.

BY PERCY G. STILES.

If a physiologist is asked what are the requisites of a normal diet he will probably reply somewhat as follows: First, it must represent an adequate quantity of available potential energy, not less than 2,000 calories for the average human adult. Second, it must contain protein (nitrogenous) food sufficient to compensate for the unavoidable daily loss of similar material from the body. Third, it must be palatable and digestible, making due allowance for personal idiosyncrasy. He will very probably content himself with these three postulates.

If the inquiry is pressed the man of science may recollect that another necessary condition of successful nutrition is a proper supply of the inorganic or mineral elements in sufficiently varied assortment. The tissues cannot be developed or maintained without chlorides, phosphates, and other saline contributions. The need for substances of this class is more urgent during the period of growth than later, but it always continues to exist. A similar statement may be made with reference to the protein of the ration; this, too, must be furnished in relative abundance and varied form during the growth of the subject and may be reduced when full stature has been reached. Mendel has shown that kind as well as quantity must be considered when protein is chosen for experimental nutrition of an animal. Proteins from certain sources suffice for maintenance only and not to minister to growth.

With the accumulation of physiological data during the past few years it has become increasingly apparent that there may be criteria for the adequacy of a diet not included in the list just given. There are now known to be organic compounds other than proteins, small quantities of which are absolutely essential to normal growth and even to continued health in the adult condition. The name of Vitamines has been proposed for all such substances. The word is well chosen in view of its root-meaning; an amine is a nitrogenous compound of a certain type and a vitamine is obviously such a

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<sup>1</sup> Reprinted from *Science Conspectus*, Vol. IV, 1914, pp. 10-13.

compound with the added distinction of being necessary to life. Casimir Funk of London has been one of the foremost contributors to the development of this conception and a valuable summary of his own work and his judgment of the work of others may be found in the *Ergebnisse der Physiologie*, Vol. XIII, pp. 124-205. (Wiesbaden, 1913.) This article is the chief source of the present abstract.

A class of serious disorders has long been known in which failure of nutrition could be named as the cardinal fact in the case and in which it has somewhat vaguely been assumed that the diet must be at fault. The most familiar disturbance of this class, at least to the general reader, has probably been scurvy. The chronicles of exploring expeditions in polar regions have contained many harrowing accounts of the ravages of this disease. It has usually been associated with the consumption of a monotonous ration, deficient in fresh vegetables and often containing a great deal of salted or canned food. Certain supplementary articles of diet, such as onions, limes, and lemons, have been credited with some power to ward off or at least to mitigate the trouble and they have been spoken of as antiscorbutics.

The victims of scurvy suffer from severe prostration, loosening of the teeth, intense soreness of the gums, friability of the bones, and a tendency to hæmorrhage partly due to a loss of the coagulating property of the blood. Those who have read the classic journals of Doctor Kane will recall the distressing situation on board his ship at the end of the Arctic winter and the commander's device to cheer his helpless men in the forecabin by setting up a mirror to bring into their midst the first sunbeam from the southern horizon. Scurvy has become less common with better supplies of food available for such parties, but it has been noted within a very few years.

Another disorder which has lately attracted much attention is beri-beri. It has its recognized centre in the East, particularly in Japan, China, Indo-China, and the Philippines. Its occurrence in Newfoundland has recently been reported. Those who suffer from beri-beri are usually the very poor and, in the Orient at least, they are people who live chiefly upon rice. In Japan the disease has been nearly eliminated from the army and navy by providing more liberal and varied rations. The symptoms are complex, but they are in general such as can be referred to the impairment of the nerves, which is known to be the most prominent physical change. There is a period of declining weight and strength and this is followed by



the development of a "multiple neuritis" with partial paralysis in both the motor and the sensory realms.

Various theories have been held with regard to beri-beri. It has been believed to be an infectious disease because it so often affects a large number of people who are closely associated, as in a prison, a ship, or a laborers' camp. The fact was formerly overlooked that such companies share the same diet and that their trouble may well be due to that source. This is now accepted as proved. But when the decision is reached that something must be wrong with the food there are still two possible views to be considered. Is the diet positively poisonous or is it merely insufficient? This question has been asked both with reference to scurvy and to beri-beri. It is not easy to answer it in such a way as to meet all objections. Nevertheless, the tendency is toward the conclusion that it is the inadequacy rather than the toxic nature of the food which is to be held responsible in these and perhaps in other cases.

It is proposed to call such failures of nutrition "deficiency diseases." It is assumed that the lack is of one or more of the specific substances already termed vitamins. The evidence in support of such a conception is especially convincing in the case of beri-beri. As long ago as 1897 it was discovered that rice which has been "polished"—that is, deprived of its pericarp or immediate husk—has a tendency to induce beri-beri and that the inclusion of the pericarp makes it entirely wholesome. It has been possible to confirm this in a striking manner by experiments on birds. If a fowl or a pigeon is restricted to polished rice as a diet it soon refuses to eat. If forced feeding is then resorted to it soon becomes pitifully weak and cannot long survive. The partial feeding is thus as surely destructive as absolute starvation. Post-mortem study of such birds shows marked degeneration of the nerves. The service of the pericarp may be conceived of in either of two ways. The polished rice may contain an active poison for which the husk provides a natural antidote. The alternative is that the pericarp furnishes a necessary constituent of the nerve tissue, a vitamin, for want of which the nerve-fibres deteriorate. How hard it is to choose between these two views has already been suggested.

Funk has been successful in his patient endeavor to isolate the vitamin the lack of which causes beri-beri. He has obtained from the pericarp of rice a number of fractions, only one of which has the remedial property. This appears to be a definite organic

body to which a formula can be assigned. It contains nitrogen but not phosphorus, an element which earlier workers had believed to be concerned. The vitamine can be separated from other foods than rice. Various animal tissues yield it and so do certain vegetables. Any kind of food which contains the vitamine may be used to supplement a ration of polished rice with the result that it becomes sufficient for the maintenance of the animal. Yolk of egg and yeast are said to have the curative power in the highest degree.

It is interesting to follow Funk's conjectures as to the systemic effects of the withholding of the invaluable vitamine. We know that in starvation the organs which cannot be spared are sustained at the expense of others. The heart and the nervous system have been found to keep their full weight to the last while tissues which are less necessary to the continuance of life are greatly reduced. Even the bones are levied upon to the extent of one-sixth of their mass. We may expect to see the same principle illustrated in the partial starvation which is at the root of any deficiency disease.

So in beri-beri it may be supposed that the vitamine which is absolutely essential to the normal nervous system is not at first confined to that part of the body. The feeding experiments have given evidence that it is present in the muscles though rather scantily. It is to be expected that in the event of failure of a supply direct from the diet the muscles will be made to surrender their store of the vitamine to replace that which has been destroyed in the nervous tissues. If we are to think that the vitamine is essential to the muscles as well as to the nerves we shall anticipate that its withdrawal will result in a disintegration of the muscle protoplasm quite out of proportion to the small amount of vitamine yielded to the preferred creditor. So for a while there will be loss of weight and strength but no marked nervous symptoms because the nerves are being kept in condition at the cost of a remorseless sacrifice of the other tissues. When the internal supply ceases to be sufficient the acute nervous effects are at once developed.

It is the opinion of Funk that both beri-beri and scurvy are prevented by the liberal use of potatoes. Before this vegetable was introduced into Europe there were severe epidemics which are believed to have been outbreaks of scurvy. The suggestion that the potato should now be added to the food-supply of the eastern countries in which beri-beri is prevalent seems a wise one. But the fact is to be emphasized that almost any diet is free from ob-

jection if it is reasonably varied. It is where poverty or some other compulsion is operative that nutritional disasters are likely.

The condition of the body in scurvy is quite different from that in beri-beri and the missing compounds are probably somewhat unlike. Some articles of diet may protect against both; some may be specific for only one. Allied with scurvy are the disorders called ship beri-beri, infantile scurvy (Barlow's disease), and the experimental scurvies which can be produced in animals by limiting the intake to a few foods. Still other pathological states may be found to have a more or less similar basis. An attempt has been made to justify the claim that pellagra is a deficiency disease, but this is strongly contested. Abnormalities of early development such as rachitis (rickets) and, perhaps, later perversions of growth such as cancer may be connected with the lack of certain chemical constituents in the income of the body. At this point it may be in order to say that the diet itself may conceivably be ideal and yet there may be a failure to utilize the vitamins offered either because of a failure to absorb them or because of the premature decomposition in the alimentary tract.

A few years ago Crichton-Browne, an English authority, in passing an unfavorable judgment upon the dietetic standards of Chittenden and others called attention to the fact that the diet approved by them seemed to correspond closely with that of the very poor. The comparison was based upon fuel value and protein content. It is now possible to modify the statement that the two are precisely equivalent. The low diet of the New Haven school is an inclusive one, while that of the poor is of limited variety. A supply of the requisite minor bodies—vitamins, if we adopt the term—is much more surely to be relied on in the first case.

Bunge, the Austrian physiologist, pointed out in 1901 that sugar is an unnatural food, in that it has been refined to the exclusion of all compounds but saccharose. Foods which are not deliberately prepared by industrial or domestic processes are always mixtures, however much one constituent may predominate. The teaching of Sylvester Graham in the first half of the nineteenth century that the foods offered by nature should not be separated into their ingredients but taken in their entirety is frequently reëchoed in our own day. In the light of studies like those of Funk it is apparent that there is a certain foundation for the idea that foods may be "denatured" either by discarding valuable fractions or by modes

of preparation which destroy essential compounds. The fear that disturbances of nutrition from such causes threaten the American people as a whole may be dismissed, but it is interesting to have a new insight into a matter which under certain conditions becomes of pressing importance.

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### PHARMACEUTICAL MEETING.

At the third Pharmaceutical Meeting held February 20th, Mr. A. K. Lobeck spoke on "A Roughing Trip Across the Continent," showing about 150 colored slides. While the subject may have seemed remotely connected with pharmacy, yet, as Mr. Poley very well brought out in his remarks afterward, anything which will attract the pharmacist's attention to out-of-door life will be a benefit to him and tend to draw him away from his confined state of existence.

Mr. Lobeck attempted throughout the story of the trip to interpret the natural scenery of the country. The origin of Niagara Falls, the fact that they are receding at the rate of 5 feet per year, the geological reason for the forms observed in the Garden of the Gods, and the explanation of the scenery around Horse Shoe Curve were some of the things dwelt upon. A summary of the trip was given showing in detail the distribution of the expenses and giving the average of expenses for each day. Exclusive of railroad fares it was shown that the average cost per day was 88 cents, this low average being accounted for by the fact that during the trip of 63 days, 27 days were spent camping or on ranches, either working or under more hospitable circumstances.

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WHAT IS SLEEP? In an article on "Sleep" Dr. Boris Sidis says: "Sleep is not a disease, not a pathological process due to the accumulation of toxic products in the brain or in the system generally. Sleep is not an abnormal condition, it is a normal state. Like the waking states, sleep states are part and parcel of the life-existence of the individual. Waking and sleeping are intimately related—they are two different manifestations of one and the same life-process—one is as normal and healthy as the other."





THE PROCTER MONUMENT. PHOTOGRAPH OF MODEL OF THE BRONZE STATUE, DESIGNED BY EDWARD BERGE, AND TO BE ERECTED IN WASHINGTON, D. C., WHEN COMPLETED.

# THE AMERICAN JOURNAL OF PHARMACY

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*JUNE, 1914*

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PROFESSOR WILLIAM PROCTER, JR.

1817-1874.

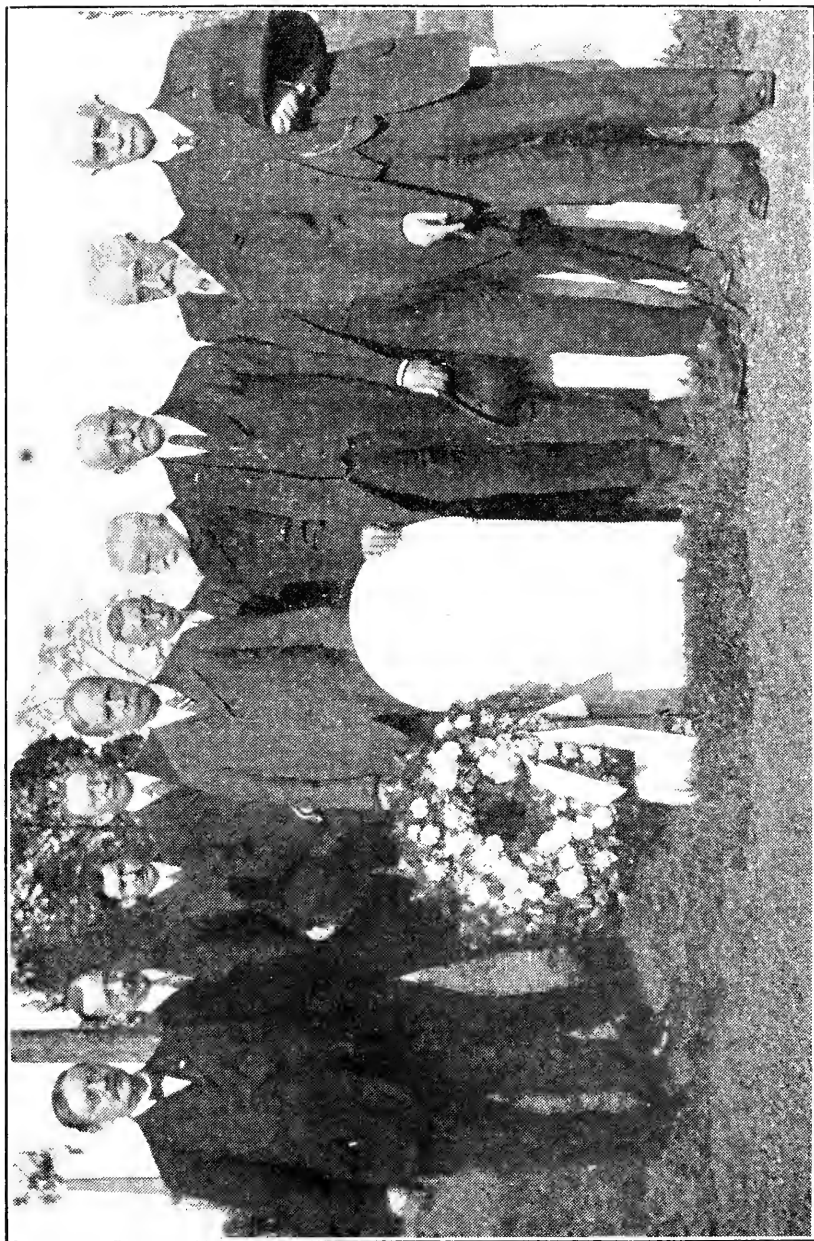
By JOSEPH P. REMINGTON.

Forty years have elapsed since the former editor of this JOURNAL passed away on that fateful night of February 10, 1874. During these forty years Pharmacy has developed by leaps and bounds; new and weighty problems have arisen and have been solved, but many more remain, and the future gives promise of still greater achievements in the profession which Procter loved.

To John F. Hancock, of Baltimore, must be given the principal credit for inaugurating and carrying to successful fruition the work of erecting a statue in bronze to perpetuate the memory of this great pioneer in professional pharmacy.

The ninety-seventh anniversary of his birthday was celebrated at the Philadelphia College of Pharmacy on May 3rd by a special meeting of his friends and former students. Reminiscences and tributes to his memory were freely uttered, followed by a dinner and a trip in the afternoon to Mount Holly, N. J., to visit his summer home and grave. Among those present were the following:

Dr. B. S. Erwin	C. B. Lowe
O. W. Osterlund	C. H. LaWall
C. A. Weidemann	R. C. Lippincott
Dr. W. H. H. Githins	Otto Kraus
Howard B. French	Henry Kraemer
J. S. Beetem	F. X. Moerk
W. Estell Lee	J. P. Remington
Thomas D. McElhenie	Edward Berge
George M. Beringer	J. F. Hancock
Adolph W. Miller	Martin I. Wilbert



[Courtesy of *American Druggist*.]  
GROUP AT THE GRAVE OF WILLIAM PROCTER, JR., IN MT. HOLLY, N. J.



Samuel M. Bines

Hugh Campbell

Dr. Henry A. Newbold

Edwin M. Boring

Dr. F. E. Stewart

E. B. Jones

Harry P. Thorn

Alexander Dubell

The special object of bringing Procter's friends together was to have them comment upon and criticise a *model* of a bronze statue which it is proposed to erect upon the grounds of the Smithsonian Institution, at Washington. The sculptor, Edward Berge, has reproduced in a remarkable manner, from photographs and very scanty material at command, a model which will serve as a starting point in the work of moulding the bronze statue.

The following resolution was unanimously passed by the meeting:

"*Resolved*, That the work of Mr. John F. Hancock in connection with the Procter Memorial be approved, and that the model and design of Mr. Edward Berge, of Baltimore, for the statue be accepted."

It is meet and right to erect statues to our honored dead, *lest we forget*, but Procter's greatest monument must ever be his great services to Pharmacy, and especially his twenty-eight years as Editor of the AMERICAN JOURNAL OF PHARMACY.

"Could each here vow to do his little task as the departed did his great one—in the manner of a true man—not for a day, but for eternity; to live as he counseled, not commodiously in the Reputable, the Plausible, the Half; but resolutely in the Whole, the Good, and the True."—*Carlyle*.

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#### THE "CLAYTON FRENCH FELLOWSHIP" IN THE PHILADELPHIA COLLEGE OF PHARMACY.

When an institution is well equipped especially for doing work which is not in the regular routine of things it seems a shame when few or none are encouraged to profit by such favorable circumstances. Our institution, owing to its long standing, the activity and friendly relations of its faculty with the outside world, has gradually accumulated apparatus and materials which, owing to the general nature of things, can be used only by those who are interested in problems external to the regular course of instruction. There is no such thing, as yet, as a post-graduate course here, but there has recently been made the first step in that direction. The fellowship

which we are about to mention will make it possible for some capable and interested student to pursue work along some particular line of investigation which would otherwise go untouched but for this stimulus. Both the student and the college will profit thereby, and there is also the chance that it may lead to some big benefit to the profession of pharmacy as a science. It is a hard enough thing to settle down to the prosaic task of fathoming out a difficult problem, and anything like this which makes it an honor and which reduces also the financial burden of such a task is almost essential to the building up of a great work.

In order to provide for fellowships, and that those who would contribute to such endowments might know to what purposes they would be applied, a new article on Scholarships and Fellowships has been incorporated into the By-laws of the Philadelphia College of Pharmacy. This article reads as follows:

" Scholarships and Fellowships covering instruction given in the College or studies pursued elsewhere by direction of its Board of Trustees, may be established by the Board of Trustees as funds for such purposes are provided.

" To found a Pharmacy Course Scholarship, a sum of not less than \$3000 shall be paid to the College. The student to whom such scholarship is awarded shall receive free instruction in all of the lectures and laboratories in the course leading up to a degree in Pharmacy for the period for which the award is made.

" To found a Special Scholarship or a Partial Pharmacy Course Scholarship, a sum of not less than \$1500 shall be paid to the College. In no case shall the sum paid be less than, when invested, will produce an income equivalent to the fees required by the College from students for similar instruction. The donor may designate the course of lectures or laboratory instruction to which such special bequest or donation is to be applied. The student to whom such Special Scholarship or Partial Pharmacy Course Scholarship is awarded shall receive free instruction in the lectures and laboratories named for the period for which the award is made.

" To found a Research Fellowship, a sum of not less than \$5000 shall be paid to the College; the income from such a foundation is to be paid to the student to whom such fellowship is awarded to pay for the tuition, materials, and apparatus used in the research work and as compensation for such aid in the laboratories, museums, library, or other department of the College as the recipient may render.

"The founder of a fellowship may designate the title of the fellowship and the special investigation, science, or department to which the research is to be directed, and may select, from time to time, the fellow to whom the fellowship is to be awarded. In the absence of such designation or selection the Board of Trustees shall decide the title and the application of the research, and, subject to confirmation by the Board of Trustees, nominate from time to time the fellow on written application setting forth the subject of research work that is to be engaged in, preference is to be given to post-graduate study in the sciences associated with pharmacy.

"If any student to whom a scholarship or a fellowship is awarded is found to be of improper character, or is deficient in mentality or scholarship, or fails to attend the instruction or to pass satisfactory examinations, the award shall be cancelled.

"A scholarship or a fellowship is awarded, in accordance with the By-Laws and Rules and Regulations established by the Board of Trustees, to the student named and for the period specified and cannot be transferred by the recipient.

"All moneys received by the College for the purpose of founding a scholarship or fellowship shall be invested by the Finance Committee in accordance with their best judgment, and a separate account shall be kept of each such scholarship or fellowship.

"If any donation or bequest received for the purpose of founding a scholarship be insufficient for the purpose intended, then such sum received shall be invested by the Finance Committee, and when the aggregate of the principal and accrued interest is sufficient for the purpose intended, the scholarship shall be established by the Board of Trustees.

"The Board of Trustees shall have authority to offer, in the name of the College, free scholarships to students of such public schools or other educational institutions as the Board may designate."

At a recent meeting of the Board of Trustees President French announced that Mrs. Mary French Banks, of Philadelphia, had donated through him the sum of \$5000 for the establishment of a fellowship as a memorial to her father, Clayton French. The Board gratefully accepted the sum and established a fellowship, to be known as the "Clayton French Fellowship." The following is a copy of the letter of transmittal to Mrs. Banks by the Chairman of the Board of Trustees:

MAY 5, 1914.

MRS. G. W. BANKS,  
Philadelphia, Pa.

*Dear Madam:*

Mr. Howard B. French, at the meeting of the Board of Trustees of the Philadelphia College of Pharmacy this P.M., presented your check drawn to his order and endorsed by him to the Treasurer of the College for \$5000 to establish a Fellowship as a memorial to your deceased father, Clayton French. Permit me to assure you the appreciation of the Board for the courtesy you have extended and the honor that you bestow upon one who many years ago was a student in this institution.

The following resolutions were unanimously passed and ordered to be forwarded to you:

"*Resolved*, That the Board of Trustees of the Philadelphia College of Pharmacy gratefully acknowledge receipt of Five Thousand Dollars (\$5000), through the hands of Mr. Howard B. French, from Mrs. Mary F. Banks, to be used in establishing a Fellowship in honor of her deceased father, the late Clayton French.

"*Resolved*, That a marble tablet be erected in the hallway of the College, bearing the following inscription:

1824

1890

Clayton French

FELLOWSHIP

Established by his daughter

Mary French Banks

May 16th, 1914

"*Resolved*, That the Five Thousand Dollars (\$5000) donated for establishing the Clayton French Fellowship shall be invested in our mortgage account, and that the income therefrom shall be used for advanced research work."

Assuring you the deepest appreciation of the Board, I have the honor to be

Yours truly,

GEORGE M. BERINGER,

*Chairman of the Board.*

## THE VOLUMETRIC ESTIMATION OF SULPHATES.

By HORACE NORTH.

Although  $\text{SO}_4$  is easily the most important acidic ion concerned in the operations of industrial chemistry, there is at the present time no satisfactory method of general application for its volumetric estimation. A method is proposed which, in the light of numerous experiments, promises to be widely useful. Subject to certain limitations which will be considered in due course, the method is applicable in the presence of the ions Li, Na, K,  $\text{NH}_4$ , Cu, Mg, Ca, Sr, Zn, Cd, Hg, Al, Ni, Co, Cl,  $\text{PO}_4$ ,  $\text{B}_4\text{O}_7$ . All data are referred to one standard solution which is readily prepared of exact strength and which is permanent. The end point of the titration is clearly defined. When all is in readiness an estimation requires fifty minutes.

In 1877 Hinman<sup>1</sup> proposed to determine sulphuric acid as follows: To a slightly acid solution of a sulphate heated to boiling is added a small excess of a solution of barium chromate in hydrochloric acid, barium sulphate is precipitated, then the solution is neutralized with ammonia which precipitates the remaining barium chromate, the precipitates of barium sulphate and chromate are filtered off, and the chromic acid, determined in the filtrate by means of stannous chloride, is equivalent to the sulphuric acid in the original solution.

This method is limited in its application; in particular, metals forming chromates insoluble in the presence of ammonia as well as phosphates and borates interfere. Various modifications<sup>2</sup> designed to correct its inherent defects have been suggested without, however,

<sup>1</sup> *Amer. Journ. Science and Arts*, **114**, 478.

<sup>2</sup> Andrews, *Am. Chem. Journ.*, **2**, 567; **32**, 476-480.

Marboutin and Molinié, *Bull. Soc. Chim.*, **17**, 950-955; **19**, 713-717. *Journ. Soc. Chem. Ind.* (1897), 1041; (1898) 874.

Reuter, *Chem. Ztg.* (1898), 357.

Telle, *J. Pharm. Chim.*, **7**, 165-170.

Bruhns, *Z. anal. Chem.* (1906), 573.

Komarowsky, *Chem. Zeit.*, **32**, 770.

Mitchell and Smith, *Chem. Soc. Proc.*, **25**, 291.

Repiton, *Monit. Scient.*, **24**, 382-384.

Holliger, *Stahl u. Eisen*, **30**, 1376-1378; *Z. Anal. Chem.*, **49**, 84-93; *Z. angew. Chem.*, **22**, 436-449.

Roemer, *Z. Anal. Chem.*, **49**, 490-492.

extending its usefulness. Thus, it having been shown that HCl is oxidized on prolonged contact with  $\text{Cr}_2\text{O}_7$ , the strength of the standard solution being thereby altered, trichloroacetic acid was proposed to hold the  $\text{BaCrO}_4$  in solution. In any case it is impossible to precipitate  $\text{BaSO}_4$  in the presence of chromate without coprecipitation of the latter in some degree. For this reason and in order, further, to avoid the uncertainty arising from the instability of solutions of barium chromate, some authors recommend separate solutions of barium and chromate, the  $\text{BaSO}_4$  being precipitated before the introduction of the chromate. Another way of avoiding the instability of acid solutions of barium chromate is to employ a mechanical suspension or cream of the salt. This idea would not seem to be in accord with good volumetric practice. Calcium carbonate has been used in place of ammonia, though with no very obvious advantages. Various means have been adopted for the estimation of the  $\text{Cr}_2\text{O}_7$ .

The volumetric solutions required in the proposed method are:

*Normal Potassium Dichromate.*—Dissolve 49.033 gms.<sup>3</sup>  $\text{K}_2\text{Cr}_2\text{O}_7$ , previously powdered and dried at  $120^\circ \text{C}$ ., in sufficient water to measure 1000 c.c.

The solution is normal with respect to oxidizing power.

*Tenth-normal Sodium Thiosulphate.*—Measure 10 c.c.  $\text{N}/10$   $\text{K}_2\text{Cr}_2\text{O}_7$  into a 100 c.c. glass-stoppered volumetric flask and make up to the mark. Measure 20 c.c. of this solution into a 500 c.c. Florence flask containing 1 gm. KI just previously dissolved in 20 c.c. dilute sulphuric acid (100 c.c. conc.  $\text{H}_2\text{SO}_4$  + 900 c.c. water), rinse down the sides of the flask with 60 c.c. water, mix the liquids, cover the flask with a watch-glass and let stand six minutes. Dilute the liquid with 150 c.c. water and titrate the free I with a solution of sodium thiosulphate (25 gms.  $\text{Na}_2\text{S}_2\text{O}_3 + 5\text{H}_2\text{O}$  in 1000 c.c.), adding starch indicator near the end. Divide 20,000 by the number of c.c. required and dilute each litre of the  $\text{Na}_2\text{S}_2\text{O}_3$  solution to the volume indicated.

The above is essentially the method of Seubert and Henke<sup>4</sup> for the iodometric estimation of  $\text{Cr}_2\text{O}_7$ .

*Third-normal Barium Chloride.*—The solution is equivalent to the dichromate solution and contains 40.72 gms.  $\text{BaCl}_2 + 2\text{H}_2\text{O}$  per litre.

<sup>3</sup> The international atomic weights for 1913 were used throughout the investigation.

<sup>4</sup> *Zeit. f. ang. C.*, 1900, 1147; "Volumetric Analysis," Sutton, 1904, 184.

Measure 4 c.c. HCl (sp. gr. 1.12), 40 c.c. water and 10 c.c. barium chloride solution (about 43 gms.  $\text{BaCl}_2 + 2\text{H}_2\text{O}$  in 1000 c.c.) into a 100 c.c. glass-stoppered volumetric flask, heat the liquid to boiling, run in 10 c.c.  $\text{N}/1 \text{ K}_2\text{Cr}_2\text{O}_7$ , rinse down the neck of the flask with 10 c.c. water and without further heating add drop by drop with constant shaking a mixture of 15 c.c. ammonia water (sp. gr. 0.98) and 2 c.c. 36 per cent. acetic acid. Cool the mixture to the normal temperature, make up to the mark and filter with the aid of suction through an asbestos felt previously formed in the usual manner, then dried at about  $110^\circ \text{C}$ . Titrate 40 c.c. of the filtrate under the conditions specified in the standardization of the  $\text{N}/10 \text{ Na}_2\text{S}_2\text{O}_3$ , except that 40 c.c. water are used in place of 60 c.c., the total volume of the solution during the six-minute period of standing being 100 c.c. Divide 20,000 by the number of c.c.  $\text{N}/10 \text{ Na}_2\text{S}_2\text{O}_3$  required, and dilute each litre of the  $\text{BaCl}_2$  solution to the volume indicated. A new trial is then to be made with, if necessary, the slight readjustment required.

An estimation of  $\text{SO}_4$  is carried out as follows:

Transfer the sulphate solution containing about 0.16 gm.  $\text{SO}_4$  to a 100 c.c. glass-stoppered volumetric flask, dilute to a volume of 30 c.c., add sufficient HCl (sp. gr. 1.12) so that the total amount present is 4 c.c. (if acidity is unknown, first neutralize with ammonia), heat the liquid to boiling, run in 20 c.c.  $\text{N}/3 \text{ BaCl}_2$ , again heat to boiling, run in 10 c.c.  $\text{N}/1 \text{ K}_2\text{Cr}_2\text{O}_7$ , rinse down the neck of the flask with 10 c.c. water and without further heating add drop by drop with constant shaking a mixture of 15 c.c. ammonia water (sp. gr. 0.98) and 2 c.c. 36 per cent. acetic acid. Complete the experiment as specified under the standardization of the  $\text{N}/3 \text{ BaCl}_2$ .

C.c.  $\text{N}/10 \text{ Na}_2\text{S}_2\text{O}_3$  required  $\times 0.008 =$  gm.  $\text{SO}_4$  originally taken.

The reaction between equivalent solutions of  $\text{K}_2\text{Cr}_2\text{O}_7$  and  $\text{BaCl}_2$  is expressed by the equation:  $\text{K}_2\text{Cr}_2\text{O}_7 + \text{BaCl}_2 + \text{H}_2\text{O} = \text{BaCrO}_4 + \text{K}_2\text{CrO}_4 + 2\text{HCl}$ . The resulting HCl retains in solution a considerable portion of the Ba. On neutralizing with ammonia all of the Ba is thrown out as chromate and half the Cr originally taken remains in solution.

A large number of preliminary experiments, the details of which it is hardly necessary to give, demonstrated the following points:

(1) When cold solutions of  $\text{K}_2\text{Cr}_2\text{O}_7$  and  $\text{BaCl}_2$  are mixed and neutralized, the precipitate of  $\text{BaCrO}_4$  carries down soluble chromate in considerable and variable amounts.

(2) The same error in less degree occurs when the  $\text{BaCl}_2$  solution is added to the diluted and boiling  $\text{K}_2\text{Cr}_2\text{O}_7$  solution and the neutralization effected at the boiling point.

(3) The error is eliminated only when the  $\text{K}_2\text{Cr}_2\text{O}_7$  and  $\text{BaCl}_2$  solutions are mixed in the presence of sufficient  $\text{HCl}$  to prevent the precipitation of  $\text{BaCrO}_4$ , and then ammonia water is added drop by drop to the hot liquid; further, the ammonia water must be fairly dilute so that not too much  $\text{BaCrO}_4$  is thrown out at once as the liquid approaches neutrality.

Acetic acid is unaffected by dichromate under the conditions of the procedure. 10 c.c.  $\text{N}/1 \text{ K}_2\text{Cr}_2\text{O}_7$  were measured into a 100 c.c. volumetric flask, 40 c.c. water and 1 c.c. 36 per cent. acetic acid were added, the liquid was boiled 1 minute, cooled and made up to the mark. 20 c.c. required 19.95 c.c.  $\text{N}/10 \text{ Na}_2\text{S}_2\text{O}_3$ . An independent experiment done in the same manner required 20 c.c.  $\text{N}/10 \text{ Na}_2\text{S}_2\text{O}_3$ .

The use of acetic acid widens the application of the method greatly. Numerous chromates insoluble in the presence of ammonia readily dissolve in acetic acid. The latter also permits of the application of the method in the presence of borates and, especially, of phosphates in limited amounts. It is highly important that the excess of acetic acid be not much greater than 0.5 c.c., which is nearly equivalent to 10 c.c.  $\text{N}/1 \text{ K}_2\text{Cr}_2\text{O}_7$ . An undue excess would exert a marked influence on the solubility of the  $\text{BaCrO}_4$  and lead to too high results.<sup>5</sup> The quantities of reagents specified are such that under the actual working conditions of the procedure the excess of acetic acid finally present is close to 0.5 c.c.

The method being designed for technical use, the volumes required to be handled are kept within moderate limits.

In the volumetric standardization of the  $\text{BaCl}_2$  under the conditions specified various errors compensate each other so perfectly that gravimetric assays show very nearly theoretical results. Obviously this fact is of the highest importance in the practical operation of the method. If this were not so it would be necessary to standardize the  $\text{BaCl}_2$  gravimetrically and apply a correction to the titration. In the course of the work two independent sets of reagents were prepared. First lot of  $\text{BaCl}_2$ : 10 c.c. yielded 0.3885 gm.  $\text{BaSO}_4$ .

<sup>5</sup> Cf. Bray, "A System of Qualitative Analysis for the Common Elements," *J. Am. Ch. Soc.*, 1909, 611-637.



equivalent to 0.4066 gm.  $\text{BaCl}_2 + 2\text{H}_2\text{O}$ . Second lot of  $\text{BaCl}_2$ : 10 c.c. yielded 0.3886 gm.  $\text{BaSO}_4$ , equivalent to 0.4067 gm.  $\text{BaCl}_2 + 2\text{H}_2\text{O}$ . Theory demanded 0.4072 gm.  $\text{BaCl}_2 + 2\text{H}_2\text{O}$ . Error = 0.1 per cent.

Ordinarily about 0.16 gm.  $\text{SO}_4$  should be taken. If, however, the proportion of  $\text{SO}_4$  is so small that 0.16 gm. cannot be taken without increasing unduly the concentration of the other ions, it is necessary to take into account the error arising from the solubility of the  $\text{BaCrO}_4$ , which, under the conditions, is represented by 0.3 c.c.  $\text{N}/10 \text{ Na}_2\text{S}_2\text{O}_3$  per 40 c.c. of the filtrate. For example, 10 gms. table salt were dissolved in sufficient water to measure 100 c.c. Volumetric and gravimetric estimations were made on 10 c.c. portions. 40 c.c. of the filtrate required 1.1 c.c.  $\text{N}/10 \text{ Na}_2\text{S}_2\text{O}_3$ . The correction having been deducted, 0.0064 gm.  $\text{SO}_4$  was indicated.  $\text{BaSO}_4$  found: 0.0152 gm., equivalent to 0.0062 gm.  $\text{SO}_4$ .

Table I presents a large part of the experimental data and is self-explanatory.

#### *Notes Supplementary to Table I.*

a. Carefully recrystallized and dehydrated by gentle ignition; purity also established gravimetrically in the course of some previous work.

b.  $\text{Cu}^{++}$  does not interfere, provided care is taken to prevent the premature formation of cuprous salt. Should this occur, the titrating fluid becomes cloudy. Shaking and standing may clear it. The  $\text{N}/10 \text{ Na}_2\text{S}_2\text{O}_3$  should be added in small portions with vigorous shaking. The first disappearance of the blue color is taken as the end. The titration may also be carried out without starch indicator, the thiosulphate being run in until there is no further change in color and the liquid acquires a slight permanent opalescence.

c. Mg occasions a positive error variable between 1 and 2 per cent. The substitution of caustic soda for ammonia does not reduce this error.

d. Two independent experiments.

e. Although  $\text{SrCrO}_4$  is readily soluble under the conditions of the procedure, the slight solubility of  $\text{SrSO}_4$  greatly limits the application of the method in the presence of Sr.

f. Less the correction  $0.3 = 2$  c.c.

g. The salt was badly effloresced.

h. The study of this element led to the addition of the ammonia and acetic acid mixed. Alumina once precipitated by ammonia redissolves with great difficulty in so weak an acid as acetic. Further, precipitated alumina occludes soluble chromate. Under the conditions of the procedure the aluminium remains in solution or, at most, the liquid becomes slightly opalescent.

i. The usual formula with  $7\text{H}_2\text{O}$  was assumed; hence the weight taken. The salt actually contained  $6\text{H}_2\text{O}$ .

TABLE I.  
*Typical Experiments on the Ions Na, K, Li, NH<sub>4</sub>, Cu, Mg, Ca, Sr, Zn, Cd, Al, Co, Ni.*

Solution	Portions taken	Volumetric			Gravimetric		Per cent. error
		N / 10	Na <sub>2</sub> SO <sub>3</sub>	SO <sub>4</sub>	BaSO <sub>4</sub>	SO <sub>4</sub>	
2.367 gms. Na <sub>2</sub> SO <sub>4</sub> <sup>a</sup> in 100 c.c.	10 c.c.	20 c.c.	0.1600 gm.	0.1573 gm.	0.3822 gm.	0.1573 gm.	0
2.904 gms. K <sub>2</sub> SO <sub>4</sub> in 100 c.c.	10 c.c.	19.6 c.c.	0.1568 gm.	0.1594 gm.	0.3874 gm.	0.1594 gm.	-0.3
1.832 gm. Li <sub>2</sub> SO <sub>4</sub> in 100 c.c.	10 c.c.	19.95 c.c.	0.1596 gm.	0.1591 gm.	0.3867 gm.	0.1591 gm.	+0.13
2.202 gms. (NH <sub>4</sub> ) <sub>2</sub> SO <sub>4</sub> in 100 c.c.	10 c.c.	19.95 c.c.	0.1604 gm.	0.1589 gm.	0.3861 gm.	0.1589 gm.	+0.31
4.162 gms. CuSO <sub>4</sub> + 5H <sub>2</sub> O <sup>b</sup> in 100 c.c.	10 c.c.	20.05 c.c.	0.1608 gm.	0.1591 gm.	0.3865 gm.	0.1591 gm.	+1.
2.006 gms. MgSO <sub>4</sub> in 100 c.c.	10 c.c.	20.1 c.c. <sup>d</sup>	0.1624 gm.	0.1600 gm.	0.3886 gm.	0.1600 gm.	+1.1
4.108 gms. MgSO <sub>4</sub> + 7H <sub>2</sub> O in 100 c.c.	10 c.c.	20.3 c.c.	0.1624 gm.	0.1600 gm.	0.3886 gm.	0.1600 gm.	+1.5
	.....	20.3 c.c.	0.1632 gm.	.....	.....	.....	+1.5
	.....	20.4 c.c.	.....	.....	.....	.....	+2.
2.269 gms. pure, pp., air-dried CaSO <sub>4</sub> + 30 c.c. HCl + water to make 200 c.c.	20 c.c.	15.6 c.c.	0.1248 gm.	0.1242 gm.	0.3017 gm.	0.1242 gm.	+0.48
Pure SrSO <sub>4</sub> <sup>e</sup> + 20 c.c. HCl + water to make 200 c.c., shaken and filtered.....	20 c.c.	2.3 c.c. <sup>f</sup>	0.0160 gm.	0.0170 gm.	0.0414 gm.	0.0170 gm.	+0.7
4.792 gms. ZnSO <sub>4</sub> + 7H <sub>2</sub> O in 100 c.c.	10 c.c.	20.2 c.c.	0.1616 gm.	0.1605 gm.	0.3901 gm.	0.1605 gm.	+1.
4.275 gms. 3CdSO <sub>4</sub> + 8H <sub>2</sub> O <sup>g</sup> in 100 c.c.	10 c.c.	22.4 c.c.	0.1792 gm.	0.1771 gm.	0.4303 gm.	0.1771 gm.	+0.1
3.954 gms. AlK(SO <sub>4</sub> ) <sub>2</sub> + 12H <sub>2</sub> O <sup>h</sup> in 100 c.c.	10 c.c.	19.85 c.c.	0.1588 gm.	0.1586 gm.	0.3853 gm.	0.1586 gm.	+0.8
3.593 gms. Al <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub> + 16H <sub>2</sub> O in 100 c.c.	10 c.c.	20 c.c.	0.1600 gm.	0.1587 gm.	0.3856 gm.	0.1587 gm.	+1.
4.686 gms. CoSO <sub>4</sub> + 6H <sub>2</sub> O <sup>i</sup> in 100 c.c.	10 c.c.	21.5 c.c.	0.1720 gm.	0.1702 gm.	0.4135 gm.	0.1702 gm.	+1.
4.380 gms. NiSO <sub>4</sub> + 6H <sub>2</sub> O in 100 c.c.	10 c.c.	19.8 c.c.	0.1584 gm.	0.1567 gm.	0.3808 gm.	0.1567 gm.	+1.

*Phosphates.*—0.5 gm.  $\text{Na}_2\text{HPO}_4 + 12\text{H}_2\text{O}$ , 4 c.c.  $\text{HCl}$  (sp. gr. 1.12), 40 c.c. water and 10 c.c.  $\text{N } 3 \text{ BaCl}_2$  were mixed in a 100 c.c. flask, the liquid was heated to boiling, 20 c.c. water were added, then drop by drop with constant shaking a mixture of 15 c.c. ammonia water (sp. gr. 0.98) and 2 c.c. 36 per cent. acetic acid was added. Near the end a considerable amount of precipitate appeared which failed to redissolve on shaking or boiling. There was much phosphate still in solution. Various other amounts of phosphate were tried under the same conditions. The results are given in Table II.

Blank<sup>a</sup> tests were done in the presence of various amounts of phosphate. The results are given in Table III.

TABLE II.

$\text{Na}_2\text{HPO}_4 + 12\text{H}_2\text{O}$ taken	Precipitate
0.5 gm. ....	Considerable.
0.3 gm. ....	Small.
0.25 gm. ....	Slight.
0.2 gm. ....	Slight.
0.15 gm. ....	Barely visible.
0.1 gm. ....	None.

Blank tests were done in the presence of  $\text{HgCl}_2$  (0.45 gm.) and  $\text{Na}_2\text{B}_4\text{O}_7 + 10 \text{ H}_2\text{O}$  (0.5 gm.), respectively. Neither substance interfered.

TABLE III.

$\text{Na}_2\text{HPO}_4 + 12\text{H}_2\text{O}$ taken	$\text{N} /_{10} \text{ Na}_2\text{S}_2\text{O}_3$ required	Per cent. error
0.5 gm.	21.3 c.c.	+6.5
0.3 gm.	20.6 c.c.	+3.
0.25 gm.	20.3 c.c.	+1.5
0.2 gm.	20.3 c.c.	+1.5
0.15 gm.	20.05 c.c.	+0.25
0.1 gm.	20 c.c.	0

*Iron.*— $\text{Fe}^{++}$  is, of course, inadmissible.  $\text{Fe}^{+++}$ , if present in the final titration, liberates I from KI and vitiates the result.  $\text{Fe}^{+++}$  may be completely removed from the solution as basic ferric acetate by boiling the liquid after adding the mixture of ammonia and acetic acid. Unfortunately coprecipitation of soluble chromate

<sup>a</sup> By blank test is to be understood a test in which equal volumes of the  $\text{K}_2\text{Cr}_2\text{O}_7$  and  $\text{BaCl}_2$  solutions are taken, as in the standardization of the  $\text{BaCl}_2$ .

occurs. The error is therefore negative and is too considerable to be neglected even in rough work. For example, the error in an experiment on ferric alum  $[\text{FeNH}_4(\text{SO}_4)_2 + 12\text{H}_2\text{O}]$  amounted to —8 per cent.

*Chromium.*—A large number of experiments was done on chrome alum. The results were much too high and very erratic. Indications pointed to the formation of chromous salts.

*Analytical Department, Lehn & Fink, New York.*

## THE PATENT MEDICINE PROBLEM.<sup>1</sup>

By M. I. WILBERT, Washington, D. C.

• The patent medicine problem, as it presents itself to American pharmacists to-day, is neither novel nor popular, and its continued growth has long since been recognized as a menace to the development of pharmacy as a desirable occupation. The business itself has developed as the joint offspring of cupidity and credulity and from a very early period has been the one object regarding which members of the various branches of the drug trade have differed on more frequently and more widely than on any other.

While it is generally recognized that the manufacture, sale and use of so-called patent medicines should be considered primarily as a public health problem, the business from the drug trade point of view also involves economic questions which cannot well be ignored and which have, at times at least, quite overshadowed all public health considerations. That the economic feature of the problem is on the increase rather than decrease is evidenced by an editorial in the *National Druggist* (1912, v. 42, p. 414) which asserts that the number of establishments engaged in the manufacture of patent and proprietary medicines in 1899 was 2,154, and in 1909 was 3,642. The value of the products at the factories in 1899 was \$88,791,000, and in 1909 was \$141,942,000, an increase of approximately 70 per cent. in ten years.

Whether the public health or the economic side of the problem is to be given the preference in the near future is a question that is well worth considering, and one which by the recent action of the

<sup>1</sup> Presented at a meeting of the City of Washington branch of the American Pharmaceutical Association, February 18, 1914.

American Pharmaceutical Association is once more set squarely before the American pharmacists for reply or action.

The patent medicine problem as it is now before the members of the American Pharmaceutical Association for discussion, was outlined in an editorial by the general secretary of the Association, in the *Journal* for April, 1913 (pp. 425-428). This editorial points out that the duty of the pharmacist to himself and to the public, in connection with patent medicines, is to define if possible the legitimate status for remedies of this kind, and to differentiate between acceptable and non-acceptable preparations.

This proposition was presented to the Council of the American Pharmaceutical Association at the Nashville meeting, and after considerable discussion it was agreed to appoint a Commission on Proprietary Remedies to consider the following general propositions:

"1. To inquire into and report to the Council from time to time upon the general subject of proprietary medicines, in their relations to pharmacy, medicine and the public health.

"2. To inquire whether any of the proprietary medicines, commonly known as patent medicines, contain alcohol or narcotic drugs in sufficient amount to render them liable to create a drug habit, or to satisfy such habits where otherwise created.

"3. To inquire whether, or to what extent, the commonly advertised patent medicines contain potent drugs in sufficient amount to render them dangerous in the hands of the laity.

"4. To inquire into the extent to which patent medicines are fraudulently advertised, or differ in properties or origin from the claims made for them, and the extent to which they are advertised for the cure of diseases generally recognized by the medical science as at present being incurable." (*J. Am. Pharm. Assoc.*, 1913, v. 2, p. 1195.)

As the Commission has, so far as known, made no report to the Council of the American Pharmaceutical Association, there is, as yet, no indication as to what will or will not be the attitude of this Commission toward the preparations now on the market or to be marketed in the future. Some idea of the stand that must be taken by the members of the Commission if they desire to make for progress rather than retrogression is evidenced by what has already been accomplished, not alone by the American Pharmaceutical Association, but also by other related organizations, particularly the American Medical Association.

Not to go too extensively into the history of the agitation relating to the manufacture and sale of patent medicines, more popularly designated as nostrums, we may well confine ourselves to the published records of the two national associations directly interested: the American Pharmaceutical Association and the American Medical Association, both organized somewhat over sixty years ago.

The American Medical Association almost annually, from the time of its preliminary meeting in the city of New York, in 1846, to its reorganization at Saratoga Springs in 1902, adopted resolutions condemning nostrums and secret remedies of all kinds, and pointed out objectionable features connected with them. Previous to the reorganization of the Association on the present basis, however, little or nothing of practical value was accomplished.

The American Pharmaceutical Association has also devoted considerable time and space to the discussion of problems connected with the manufacture and sale of patent and proprietary remedies. A cursory review of the proceedings of the Association suggests the rather interesting fact that this agitation appears to have developed in cycles and to have been markedly acute in decennial waves, the maximum height of the agitation being evidenced in the early years of the decennium. Thus, beginning with the Proceedings for 1853, the second meeting of the Association, we find the following resolution, which was, on motion of Joseph Laidley, substituted for one previously offered by C. B. Guthrie, and adopted by a majority of the members present:

*“Resolved*, That the American Pharmaceutical Association believes that the use and sale of secret or quack medicines is wrong in principle and is in practice attended with injurious effects to both the profession and the public at large, and believes it to be the duty of every conscientious druggist to discourage their use.

*“Resolved*, That this Association earnestly recommend to our pharmaceutical brethren to discourage by every honorable means the use of these nostrums; to refrain from recommending them to their customers; not to use any means of bringing them into public notice; not to manufacture or to have manufactured any medicine, the composition of which is not made public; and to use every opportunity of exposing the evils attending their use, and the false means which are employed to induce their consumption.” (*Proc. Am. Pharm. Assoc.*, 1853, p. 17.)

The agitation in the next decennium was largely centered about the manufacture of fluid extracts and the development of proprietary rights in preparations of this type, and ten years later we find a similar line of activity developing in connection with elixirs, which at that time were so popular. At the end of another decennium, however, the attention of members of the Association was again directed to patent medicines of the nostrum type by a resolution offered by Prof. A. B. Prescott, of Ann Arbor, to the effect that a committee of three members be appointed to agree upon the most feasible and suitable legislation to secure a sufficient statement of the composition of proprietary medicines, on the package of the same, and the more feasible and efficient action to be taken by the Association in regard to the matter. The committee appointed consisted of Albert B. Prescott, Frederick Hoffmann and Charles Rice. This committee, at the succeeding meeting of the Association, presented a lengthy report on the nature of desirable legislation regarding the manufacture and sale of proprietary remedies, and also a draft of an act regulating the sale of proprietary medicines. The committee in its report offered a resolution which was subsequently adopted by the members of the Association present, to the effect "that it is the deliberate opinion of this Association that the labels of proprietary medicines ought to carry a statement of their constituents." (*Proc. Am. Pharm. Assoc.*, 1885, v. 33, pp. 394-398.) As evidence of the need for action along these lines the committee said in part:

"All medicines, and articles used as such, concern the health of those who use them and put dependence upon them. By action or failure of action, a medicine is liable to prove hurtful when misapplied. Therefore, it is the right of a purchaser of a medicine to receive information of its constituents, their names and proportional quantities. And it is a legitimate act of the State—so far as it deems expedient—to see to it that such information, in printed form, is placed upon each package of articles of medicine, as a condition of their legal sale.

"Moreover, legislation requiring the composition of medicines to be given to the consumer is entirely in accord with the spirit of the institutions of the United States, because it is legislation tending to secure him in the means of self-preservation. The purchaser of a medicine is provided with a record of its constituents, given in terms defined by published standards: now he may guide himself,

in his own discretion or with professional aid, by the information given in the record of constituents, or he may neglect to so guide himself, and depend upon advice given on the wrapper of the medicine, in the exercise of his personal responsibility. The State has done its duty, and given the individual the opportunity for the exercise of discretion. The opportunity has an educational value to the individual."

The following year the Committee on Legislation, in its report of progress (*Proc. Am. Pharm. Assoc.*, 1886, v. 34, p. 10, 154, 155), included a resolution to the effect that:

"WHEREAS, All medicines concern the health of those who use them; and

"WHEREAS, The purchaser of a medicine selected by himself has the right to receive information of its constituents and their quantities; and

"WHEREAS, The report and the draft of a law regulating the sale of proprietary medicines, which were accepted by the American Pharmaceutical Association at its meeting held in September, 1855, embrace a method whereby the above-mentioned objects may be secured; therefore, be it

"*Resolved*, That the President and other officers of the Association be authorized and instructed to present printed copies of the reports and of the action had in this Association upon said reports, to the Governors, to the Speakers of the Senates and Houses of Representatives, and to the State Boards of Health, of the different States of the United States; also to offer any services wherein these authorities may consider the coöperation of this Association desirable or useful."

This preamble and resolution was vigorously discussed and a motion that they be stricken from the minutes of the Association was defeated. The report of the Committee was then on motion accepted, and finally on motion of C. Lewis Diehl, seconded by C. S. N. Hallberg, the preamble and resolution were adopted.

Despite the endorsement given the report of the Committee on Legislation, little or nothing of a practical nature appears to have been done. During the early years of the succeeding decade a few isolated papers on patent medicine abuses, from a public health point of view, were presented, but their readers found no following and the resolutions they offered appear to have been overlooked or ignored, while much of the time of the Association was devoted to the dis-



cussion of a plan or plans to remedy the "cutting of prices." The seriousness with which time was wasted on the discussion of the several plans that were suggested at that time serves well to illustrate the comparative importance that has been accorded the purely economic side of this problem by various branches of the drug trade.

At the semi-centennial meeting of the American Pharmaceutical Association, in 1902, several papers were again presented, bearing on existing abuses in connection with patent and proprietary remedies. These papers dealt principally with the abuse of so-called proprietary medicines and their use by physicians, and perhaps contributed somewhat at least to the renewed interest on the part of the American Medical Association in matters relating to the use of secret or semi-secret remedies by medical practitioners.

At the meeting of the American Medical Association in New Orleans in 1903, a number of papers were presented criticising medical journals for the nature and kind of advertising carried by them, and a resolution adopted by the then Section on Materia Medica and Pharmacy condemned much of the advertising then carried in the *Journal* of the Association itself. At this meeting of the Association provision was also made for pharmaceutical membership in the American Medical Association, and at the meeting in Atlantic City the following June a number of pharmacists were elected and the discussions on materia medica subjects, with the resolutions adopted at Atlantic City in 1904, no doubt were directly responsible for the inauguration of a Council on Pharmacy and Chemistry, the object of which was to endeavor to differentiate between good and bad proprietary remedies used by or offered to physicians.

A preliminary meeting of persons interested was held in Philadelphia on December 29, 1904, and the Council itself was organized in Pittsburg on February 11, 1905. This Council was immediately set to work and by June of the same year the comprehensive and at that time startling report on the acetanilide mixtures was published in the *Journal of the American Medical Association* and, as was expected, precipitated the wrath, not alone of pharmaceutical manufacturers, but also of medical journals that depend so largely on their advertising pages for existence. The so-called acetanilide report served, however, to arouse the better class of medical men to an appreciation of their duty as professional men and the endorse-

ment thus secured has contributed much to maintain the Council despite the attacks of moneyed interests within and without the membership of the Association.

The work of the Council was later in the year efficiently augmented by the series of articles originally published in *Collier's Weekly*, by Samuel Hopkins Adams, on the "Great American Fraud," and subsequently reprinted in pamphlet form by the American Medical Association. The Food and Drugs Act of June 30, 1906, also contributed its share in support of the work of the Council. These several agencies have been further augmented by the stand taken by the Commissioner of Internal Revenue in regard to alcohol containing nostrums and by the assistance given by various state officials entrusted with the enforcement of local food and drug laws, so that at the present time there is considerable evidence to show that the efforts of the Council on Pharmacy and Chemistry have made a distinct impression on thinking laymen as well as on the more progressive members of the American Medical Association.

Following the inauguration of the Council on Pharmacy and Chemistry, the American Medical Association organized a chemical laboratory in the Association building, and this laboratory, in addition to the work on "proprietary remedies," has devoted considerable time to the examination of so-called "patent medicines" or "nostrums." The resulting analyses are usually published in the *Journal* and have been in part, at least, compiled in book form in a volume entitled "Nostrums and Quackery."

This book has recently been reprinted in enlarged form, and its increasing circulation among well-informed laymen will contribute much to a better understanding of the patent medicine problem from a public health point of view, and should serve to prevent any possible retrogressive action on the part of the American Pharmaceutical Association as an Association.

In summing up this brief and admittedly incomplete survey of recent accomplishments to solve the "patent medicine" problem, it would appear that the questions involved are not to be considered as being answered until they are answered correctly, and that from the point of view of the public the influence of "patent medicines" on the health and welfare of the individual is the only factor deserving of consideration. Bearing this latter fact in mind, it would appear desirable that all branches of the drug trade give the patent

medicine problem renewed and serious consideration, and make an honest effort to adjust their interests in accord with the interests of the public and thus effectually counteract the frequently made assertion that the economic questions involved must outweigh all others so far as the drug trade may be concerned.

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## A PLEA FOR MORE EFFECTIVE CO-OPERATION AMONG PHARMACEUTICAL ORGANIZATIONS.

By W. B. DAY.

Even a superficial observer of pharmaceutical affairs must have been struck by the increase in the number of organizations which depend upon pharmacists for their membership. Not only have we the two great national associations but each commonwealth is more or less thoroughly organized with its state, county and city associations.

At first glance this situation appears most encouraging and seems to show an appreciation of the value of these organizations and a commendable spirit in affiliating with them and sharing their endeavors and their advantages, but when we look into the matter more closely we find that with all these opportunities for affiliation with an active society, the majority of pharmacists remain indifferent.

There are nearly fifty thousand drug stores in the United States and probably over seventy-five thousand qualified pharmacists. Less than five per cent. of these are members of the American Pharmaceutical Association, and certainly not more than twenty per cent. are members of the National Association of Retail Druggists. Very few state associations include within their membership more than a fifth of the qualified pharmacists of their respective states.

In some of the larger cities strong local associations exist, but, on the other hand, there are many counties and cities where organization has never been effected, or if effected has perished through disuse and neglect. Contrast with this the situation in Great Britain, where, of all European countries, the conditions most resemble our own. The last report of the Registrar of the Pharmaceutical Society of Great Britain shows 7788 members out of 16,608 qualified pharmaceutical chemists and chemists and druggists. Allowing for those who have retired from business or are engaged in some other line

of work, it is estimated that nearly two-thirds of the chemists and druggists of Great Britain are members of the national society. And the membership is growing steadily; the increase has been twenty-five per cent. during the last ten years.

The only reason for the existence of any organization is service to its members and to the profession which it represents. Are present conditions favorable to such service? Is there not a wasteful duplication of effort? Should there not be a better correlation of organized pharmaceutical activities?

Pharmaceutical associations have done wonderfully well in legislation, in education, in the development of scientific pharmacy and in the spreading of a knowledge of both technical and business methods. Co-operation has solved many perplexing questions: dangers have been bravely faced, evils have been overcome, and yet a start has scarcely been made.

The attention of pharmacists has often been called to the changing conditions which vitally affect our calling. Not only are these evidenced by the spread of commercialism, the development of chain stores and syndicates, the increased dispensing by physicians and the multiplication of hospitals and dispensaries, but, deeper than these—the drift of social legislation which in Great Britain has produced the National Insurance Act and in Germany has resulted in a state-controlled industrial insurance. We may as well face the possibility, if not the probability, of state-paid medical service, including state-furnished medicines in our own country, during the next generation. Judging from the lack of recognition accorded to pharmacists in our army, we are held in but low esteem by the federal government at the present time: physicians, dentists and even veterinarians rank far above us in the largest arm of the government service.

It is high time that all pharmaceutical organizations should carefully consider a general affiliation and correlation such as shall assign to each its special field and avoid the present overlapping and duplication. More effective work will be possible only through such mutual relations, and will deserve and receive wider support by pharmacists. A united body of seventy-five thousand pharmacists would command respect and insure fair treatment in the coming readjustment and division of labor that is sure to come as a part of the social movement.

## EFFICIENCY IN DRUG STORES.

By C. C. HONSAKER, P.D.

This is the age of specialization. Lawyers, doctors, mechanics and ministers are specialists; when needed they are consulted, they need and consult one another. We all recognize that no one man knows it all. Just as there are sick people that need competent counsel, so there are sick businesses that need attention from experts.

The old time business expert was and is, in fact, somewhat like the old-time doctor. He administered tonics and palliatives instead of getting at the seat of trouble.

By keeping records and making tests, chemists, pharmacists and physicians have been able to standardize certain medicines.

It has been but recent, however, that the business doctor was able to diagnose and apply a standardized remedy, or specific, to a sick business.

This, however, has been accomplished by the two great efficiency engineers, Emerson, of New York, and Taylor, of Philadelphia. These men have gathered together the threads of activity, and woven them into the science known as efficiency. Efficiency means the ability to accomplish. Personal efficiency is the mental and physical ability to find, and take, the best, easiest, and quickest way to the desirable things of life.

These principles are not new, you and I employ them every day, at least some of them.

Just as Sheldon has analyzed the sale, so has Emerson analyzed the operations and procedures of hundreds of successful men, and found that thirteen (13) principles were involved, in part or whole, by them in their accomplishments.

There are seven (7) practical principles, and six (6) ethical ones. To-day we will be concerned with the practical ones only.

A sick business like a sick body always has one symptom that gives the most trouble, from which, tracing backward, the cause can be located by the trained expert. You all know what this symptom of unscientific business is in the drug world. The rancorous sore in the side of the drug business is the long hours. This, however, is only a symptom or effect. The cause is much deeper.

This thirteen (13) to fifteen (15) hour day is driving the best

men out of the business. The great cry of the retail druggist is, "that we cannot get competent men."

The P. C. P. and other colleges give men good scientific training, which most of them never have an opportunity to use. The drug journals contain article after article about building up business; these are read, possibly, but seldom put into actual practice. The various organizations ask for action and attendance, but get little or none, although the advantages to be gained are obvious. Tradition has established a routine in the drug store, which very few have been able to break away from, and those who do are usually condemned.

There is no hope for the man who works thirteen (13) to fifteen (15) hours a day. It's a losing game every way one looks at it.

The philosophy of the business must be changed. It must be studied from the standpoint of the sale.

Business is buying and selling. Selling is our objective point. Our drugs and merchandise must be organized toward making the sale. The sale is the point from whence the money comes. Sales and quick ones. The five (5) and ten (10) cent stores are based on the principle of small, quick sales. Your average sale in the drug store is from fifteen (15) to eighteen (18) cents.

Efficiency, then, is the keynote. It is the only salvation. Mr. Emerson would probably try to pull the manager out of the mass of details first, so that he, the manager, could get a perspective of his business. So we will, on that assumption, try and apply the seven (7) principles to the manager first, since a business is but the lengthened shadow of a single individual.

There is one thing that the druggist is fortunate in having, and that is twenty-four (24) hours a day. The trouble is that he does not use it advantageously. Twenty-four (24) hours, then, is a fixed quantity, fixed and unchangeable. Time is what we are trying to save, therefore we will use it as our basis.

### *Standards.*

The first principles of scientific management is "Standards." A standard is a reasonable attainable maximum of desirability. Before standards can be established, however, many records must be made.

A record is anything that gives information of any kind. Records play an important part in everything we do. Baseball furnishes an excellent example of the use of records.

What we want, then, is a record of what the druggist does with

his fourteen (14) hours each day. This is accomplished by the use of a special chart, conveniently divided into five (5) minute periods or squares. The efficiency engineer keeps an account of every five (5) minutes of the fourteen (14) hours, for a period of time, say for one (1) week. At the expiration of the allotted time the various minutes are classified, wasted time analyzed, and a standard established for each of the various operations.

Possibly he filled fifty (50) prescriptions during the week and expended approximately thirteen (13) hours. The standard time, then, for filling one (1) prescription is fifteen (15) minutes under normal conditions.

You will say that it is impossible to establish a standard for such a changeable and indefinite operation. That is what they all say. If it were easy it would have been done long ago. It can be done with a complex operation, having many factors, as well as with the simpler operations, such as shoveling, shaving or even writing your name.

You now have an annotated topography of your duties. Your next move is to organize the operations into logical sequence. That brings us to the second principle.

#### *Planning.*

You now plan your operations. This you can do intelligently, since you are dealing with known facts. At this point of the reorganization your business policy changes. You become the power behind the business. The customer, doctor, salesman and others cease to mould your business to suit them. You are becoming aggressive. You know how long it takes to make a sale. You make the sale and get away. The salesmen come and go when you say; not when they want to.

To plan, though, is not enough. The Pennsylvania Railroad might plan to run the twentieth century limited from New York to Chicago; but, unless schedules were made, this plan would be useless. One crew might run at breakneck speed and send the train to the junk pile; another so slow as to consume unnecessary fuel. So, in order to avoid those conditions, definite schedules are carefully made. Consequently, the next principle to be applied is schedules.

#### *Schedules.*

A plan is a general statement.

A schedule is a definite itemized statement.

So, now, each operation is looked after minutely, a definite time

for its beginning and completion established. Everything in the store is now beginning to organize itself toward carrying into effect this new element of activity. Everything must fall in line. You do not wait for anything. Your motive is based upon known facts, and you know that you are right.

To be scientific there must be a way of showing results. There is, and it is calculated by the following method.

Divide the actual number of hours employed by the standard number, and the result is your efficiency of supply, *e.g.*, say the time wasted by various leaks to be three hours, and your standard is fourteen hours, the actual number of hours employed is the difference between fourteen hours and three hours, or eleven hours. This eleven hours divided by the fourteen hours gives  $\frac{11}{14}$ , your per cent. of efficiency of supply.

However, a man may be 100 per cent. efficient in supply of time, and yet not be efficient in the use of time, *e.g.*, a pharmacist spends thirty minutes in compounding one prescription. His standard accomplishment for thirty minutes is two prescriptions. Actual accomplishment, which is one prescription, divided by standard accomplishment, which is two prescriptions, shows his usage of time to be 50 per cent.

These same principles, remember, apply to equipment and material as well as time. You may be efficient in supply and not in use. You may be efficient in use and not in supply. You attain maximum efficiency only when you are efficient in both. This is calculated as end efficiency. End efficiency is computed by multiplying your supply of time efficiency by your efficiency of use.

The next principle is *despatching*.

Planning, as you have seen, means looking ahead, deciding what is to be done, how much time is to be allotted the stunt, and what material and equipment are necessary to its accomplishment.

Schedules assign to each stunt a definite time and place, and definite quantities and qualities of material. They also list the equipment necessary, both as to quantity and place, and the standard time for the operation of equipment. It is not enough to establish standards for time, material and equipment. It is not enough to plan ahead. It is not enough to write schedules, no matter how elaborate and perfect they may be.

You must have action. In other words, the work or stunt must be despatched. Some of the well known examples of despatching



are the umpires at a professional baseball game, the directing "next" of a porter in the barber shop, and the train despatcher.

The antithesis to despatching is procrastination.

Procrastination is nearly always due to a tired body or brain; again, the accusing finger points to the long hours. How can a man despatch an important operation or communication who is submerged by multifarious details? A train despatcher as well as an umpire must be up and above the thing he is directing.

Connie Mack's method of directing from the bench is better than the old style of directing from the field.

The principle of despatching is a simple one. It means that when the time comes to do a thing you should have everything on hand and prepared to do it, and do it.

#### *Standardizing conditions.*

This is the fifth principle of efficiency. This is the principle which is universally misapplied and misconstrued to mean efficiency. Mention efficiency to the average druggist and he will tell you that he has the most efficient store in town. What he means is that he has systematized his store from a certain standpoint. Efficiency implies system, but system does not by any means imply efficiency. You can do a thing systematically wrong.

From the moment the first principle is applied you began rearranging and standardizing conditions. This is an indication of the interdependence of the thirteen principles.

By learning each of the thirteen principles you apply the fifth principle consciously, and, therefore, more fully and effectively.

There must be a place for everything, but that place can only be found after many trial conditions. At this point I wish to call your attention to the greatest loss in the drug business. The druggist finds himself doing many things which could be done by subordinates; such as dusting, running errands, looking up phone numbers, selling stamps, dispensing soda water, etc. While learning the business he did not mind doing it, because he looked forward to the time when he would take on larger responsibilities. The time came with the responsibilities, but the menial labor remained just the same. How can a man, who fills the capacity of a menial, command respect? Justice to all includes justice to self.

There are thousands of five and ten cent sales made in the drug store. You cannot afford to waste energy making them. They must sell themselves. They are what might be termed trailers, such as

corn cures, epsom salts, seidlitz powders, etc. You can only afford to spend energy on larger sales.

This capacity to assign yourself, subordinates, material, etc., is calculated as efficiency of assignment. Consult your records, find the most profitable hour of employment. This is your standard worth for an hour. For example, suppose that for a given hour your efficiency of supply was 91.7 per cent.; in other words, that you profitably employed forty-five minutes out of the sixty in that hour. Your efficiency of use was 85 per cent.; in other words, you folded, labelled and packed eighty-five seidlitz powders during that hour, where your standard number for that hour should have been one hundred. The end efficiency of supply and use, therefore, was eighty-hundredths of 91.7 per cent., or about 78 per cent. Since a girl might have folded, labelled and packed those eighty-five powders in forty-five minutes, and her wages for the forty-five minutes would have been twenty cents, the actual commercial value of what you accomplished during that hour was twenty cents. For the purpose of illustration, let us fix your standard worth at \$1.00 for the hour. Twenty cents is 20 per cent. of \$1.00; this is your efficiency of assignment for that hour. Your end efficiency for supply, use, and assignment is therefore  $85 \times 91.7 \times 20$  per cent., or 15.5 per cent.

Efficiency of assignment is measured by the ratio between actual value of what is accomplished or produced in a given time or from a given material or a given equipment and the standard value of production for such time, material or equipment.

All the work in learning and applying the first five practical principles of efficiency has been not only leading up to the sixth principle, but actually compelling you to apply it.

The sixth principle is *standardized operations*.

It is obvious that there is only one best, easiest and quickest way to do any given thing.

There may be one hundred different ways of doing a thing. This brings the case under the mathematical law of probability. The *chance* that you may happen upon the one best, easiest and quickest way is only one in a hundred. To show how slight are the chances of happening to choose the right operation, Mr. Emerson cites the case of an executive whose work he was called upon to study. This man's working day was fifteen hours, and he was always "terribly busy." As he did not plan his work, but simply turned feverishly from one task to another as they presented themselves, he wasted

twenty-five per cent. of his time. This reduced his efficiency of supply to 75 per cent.

Because he worked too many hours a day to maintain a standard condition of health and mental vigor, he not only procrastinated, dragged his work and kept others waiting, but made many blunders. The correction of these, where correction was at all possible, consumed a great deal of time. Taking into consideration his slow accomplishment, subtracting the amount of time wasted in correcting blunders, and the amount of time consumed in doing things wrongly, which could not be corrected, his efficiency of use was greatly reduced. Since he was too busy and too harassed to plan his work, he did not standardize any of his conditions or operations, leaving these matters entirely to chance, with the result that his efficiency of use of time was only 60 per cent. Because he did not plan or study, it naturally resulted that he spent a great deal of his time doing unnecessary things, as, for example, keeping records, that were neither immediate, reliable, adequate nor permanent. He also wasted hours blundering along with trivial details that ought to have been unloaded upon a subordinate who would have done them far more efficiently.

For these reasons his efficiency of assignment was only 40 per cent., and his end efficiency ( $75 \times 60 \times 40$ ) was 18 per cent. By means of the thirteen principles of efficiency he might have accomplished just as much with far better quality in three hours as he had been accomplishing in fifteen hours. You know an analogous case.

To get back to standardized operations. This is the phase of efficiency that you mostly read about in the magazines; it involves time and motion study.

Without going into detail, I have tried to give you a perspective of the application of the principles of efficiency. This skeletonized elucidation leaves many questions unanswered that will naturally arise in your mind concerning their application to the drug business. You may not be able to see how they could possibly be applicable in the face of so many uncertainties, such as occur in the drug business.

Like a Socialist I answer by saying that those uncertain obstacles would not exist under proper management. The drug business to-day is governed by outside influences. The task we have is to regain control and manage according to a definite business policy.

You do not know what to charge for a prescription, because you have not standardized the operation of compounding. It is difficult, that is why it has not been done, but it *can* be done.

The seventh and last practical principle is written standard practice instructions. School text books, periodicals and the pharmacopœia are written standard practice instructions.

It is a difficult thing to change one's style of doing anything; therefore, it is necessary to strike a form, and to do this definite instructions must be carefully followed until it can be done with little or no conscious effort.

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## PROGRESS IN PHARMACY.

A QUARTERLY REVIEW OF SOME OF THE MORE INTERESTING LITERATURE RELATING TO PHARMACY AND MATERIA MEDICA.

By MARTIN I. WILBERT, Washington, D. C.

Interest in matters relating to pharmacy appears to be about equally divided between progress in the revision of the Pharmacopœia of the United States and matters relating to legislation designed to further restrict the sale of opium, cocaine, and other potent or habit-forming drugs.

Two additional instalments of abstracts of proposed changes with new standards and descriptions for the United States Pharmacopœia, ninth revision, have been published and distributed. The first of these, a pamphlet of 59 pages, designated Part II, embraces most of the drugs of vegetable and animal origin and presents more comprehensive changes than any one of the other instalments of changes so far published.

The *Chemist and Druggist*, London (1914, vol. 84, p. 565), in commenting on the proposed changes in the pharmacognosy of the U. S. P., voices the opinion that the general indications are that the monographs in the U. S. P. IX will be quite an advance upon those included in the present Pharmacopœia.

Part III of the abstract of proposed changes embraces most of the waters, solutions, spirits, extracts, fluidextracts, resins, tinctures, and miscellaneous galenicals. Pharmacists generally will be pleased to learn that all of the important changes proposed for the several official galenical preparations can be adequately reflected in somewhat

less than 29 printed pages. This fact would appear to indicate that many of the official formulæ have been found to be satisfactory and that the members of the Executive Committee of Revision have exercised due care in the making of changes.

Commenting on the recently published abstracts of laws regulating the production, sale, and use of poisons and habit-forming drugs in this country, the *Pharmaceutical Journal*, London (1914, vol. 92, p. 278), says:

The poison legislation of the United States consists of a multiplicity of statutes of a not very effectual character, and a fundamental alteration of the law seems to be desired. During the year 1912-1913, over forty State, territorial, or similar Legislatures were in session, and nearly if not quite all of these bodies enacted some form of legislation designed directly or indirectly to affect the sale and use of poisons. But, notwithstanding this abundance of legislation, the poison laws of the United States are admittedly still far from perfect.

"*The Harrison anti-narcotic bill*, so-called, is still pending in the Senate, with some probability that the original bill in a slightly amended form will become law during the present session of Congress. It is perhaps unfortunate that the subject of Federal anti-narcotic legislation has been unnecessarily complicated by the introduction of a number of amendments that can in no way assist in developing the primary object of the bill and will at best serve to complicate its enforcement should it become law."

*Boylan Bill*.—The recently enacted New York State law, known as the Boylan Bill, prohibits the sale of habit-forming drugs except on the prescription of a licensed physician, but the provisions do not apply to the sale of domestic and proprietary medicines actually sold in good faith as medicines and not for the purpose of evading the law, "providing such remedies or preparations do not contain more than two grains of opium, or one-fourth grain of morphine, or one-fourth grain of heroin, or one grain of codeine, or ten grains of chloral or their salts in one fluidounce, or if a solid preparation in one avoirdupois ounce, nor to plasters, liniments, and ointments for external use only." If the prescription calls for more than four grains of morphine, thirty grains of opium, two grains of heroin, six grains of codeine, or four drachms of chloral, the authority for the prescription must be verified.—*Pharm. Era*, 1914, vol. 47, pp. 199, 200.

*International Opium Conference.* (Editorial.)—Discusses a report on the correspondence respecting the second International Opium Conference. It appears that Greece has refused to sign without stating any reason, while Turkey has refused to take any part whatever in the Conference. Germany and Russia were also not ready to ratify the Convention, although they have signed. In spite of these facts it is claimed by the delegates that matters have advanced considerably and that a long step has been taken toward the attainment of unanimity.—*Chem. and Drug.*, 1914, vol. 84, p. 458.

Commenting on the above, Xrayser II (p. 491) says: "The Opium Convention, like Mahomet's coffin, is suspended between heaven and earth, and while in that state of suspense it is worthless as an instrument for any practical purpose. But while the Convention itself may fail as an administrative force, I hope its educational value will not be lost sight of, and that we as chemists will do what we can, each in his own sphere, to limit the evils which the Convention in its essential features was intended to abolish. There always will be a legitimate demand for and use of cocaine and morphine, and there will also probably always be an illegitimate demand. If we conscientiously set ourselves to discourage the latter by a judicious method of satisfying the legitimate use of these drugs, then the evil, so far as we are concerned, will be as effectually scotched as it would be by the adoption of the most stringent legal enactments." •

*Drug Addicts.*—Brown, Lucius P., is quoted as saying: "The anti-narcotic law going into effect recently is serving to uncover a terrible state of affairs. Already we have issued 1360 permits in the State, a large proportion of these to Nashville people, allowing druggists to sell them narcotics for habit use. While one-quarter of a grain twice a day is sufficient for the non-user of morphine, it requires eight grains daily for the person with the habit. Those who are on our books as having permits use an average of 251 grains a month."—*Pharm. Era*, 1914, vol. 47, p. 233. See also *J. Am. M. Assoc.*, 1914, vol. 62, p. 1427.

*Price Maintenance.* (Editorial.)—Considerable interest is being manifested at the present time in H. R. 13305, a bill introduced by Representative Stephens, of New Hampshire, which is entitled: "A Bill to Prevent Discrimination in Prices and to Provide for Publicity in Prices to Dealers and to the Public." This bill has been endorsed by the American Fair Trade League and a number of re-

tail organizations, and seeks to legalize contracts between manufacturers and dealers in articles of commerce produced under a trade mark or special brand. If enacted into law the bill would restore to manufacturers the rights supposedly existing under which the various contracts were developed in connection with the sale of so-called patent medicine.—*Pharm. Era*, 1914, vol. 47, pp. 145, 146.

*Annual Meetings.*—The annual meetings of State and National Pharmaceutical Associations and of other related organizations are attracting considerable attention. This year the order of holding the two National Drug Association meetings will be reversed: the 16th Annual Convention of Retail Druggists is to be held in Philadelphia, August 17-21, and the 62nd Annual Convention of the American Pharmaceutical Association is to follow, in Detroit, August 24-29, 1914.

*American Chemical Society.*—The meeting of the American Chemical Society was held in Cincinnati, April 7-10. Fully 1500 chemists attended and more than 150 papers were read before the various sections.

*Meeting of the American Medical Association.*—The meeting of the American Medical Association this year is to be held in Atlantic City, July 22-26. The preliminary program published in the *Journal*, May 16, 1914, contains an unusually interesting list of promised contributions. The Section on Pharmacology and Therapeutics will meet in the gymnasium of the Grammar School, on Ohio Avenue, and the program for this section, as usual, includes a number of papers of direct interest to pharmacists. The exhibition, both scientific as well as commercial, will be held in the Atlantic City Exhibition Building, corner of Kentucky Avenue and the Boardwalk. The scientific exhibition particularly promises to be unusually interesting, in that an effort will be made to present the material in a collective form so as to be more readily studied.—*J. Am. M. Assoc.*, 1914, vol. 62, pp. 1592-1609.

*The Pharmacist and Pure Drugs.*—A recent article in *Public Health Reports* (1914, vol. 29, pp. 1137-1144) calls attention to the reported results of analyses of a number of widely-used drugs and preparations, and points out that the proper enforcement of laws designed to regulate the practice of pharmacy, in conjunction with pure drugs laws, should relieve physicians and the public of any doubt as to the composition, purity, quality, and strength of all drugs and medicinal preparations used in the treatment of disease. Any-

thing short of this is a reflection on pharmacy as a calling and should not be tolerated or allowed to continue.

*Laboratory Equipment of Pharmacists.* (Floyd, Henry B.)—Some of the balances found in Washington drug stores were not sensitive to a grain, while others required a decided overweight before they would operate at all. Many of the weights used are inaccurate, having been allowed to corrode or to collect dirt. Pharmacists are known to use avoirdupois and apothecary's ounces interchangeably without regard to their difference. Glassware, especially that of less experienced manufacturers, is frequently inaccurate.—*J. Am. Pharm. Assoc.*, 1914, vol. 3, pp. 569-571.

*Weights and Measures.* (Editorial.)—In enforcing the weights and measures statutes in various States the officials report some peculiar conditions in connection with the metrological equipment of drug stores. Of particular interest is the fact that many instances are reported of over-size measuring glasses and heavy weights. These can be accounted for in only one way: the druggist has been imposed upon by the dealer from whom the inaccurate weights and measures were obtained. It behooves pharmacists to see that their weights and measures are accurate, and that none but accurate weights and measures are used. No legal requirement should be necessary to assure the proper weighing and measuring of the components of a prescription.—*J. N. A. R. D.*, 1914, vol. 18, pp. 262, 263.

*Annual Reports of the Chemical Laboratory of the American Medical Association, Volume 6.*—This little book of ninety-eight pages presents a report of the work done from January to December, 1913, and includes reprints of contributions, reports abstracted from the *Journal*, and reports not previously published. In addition to the work growing out of the investigations by the Council on Pharmacy and Chemistry, the laboratory's work includes the examination of "patent medicines," and the investigation of chemical questions connected with the Propaganda and the Queries and Minor Notes work of the *Journal*.

*"New and Nonofficial Remedies."*—A book review of "New and Nonofficial Remedies" says that this book is a valuable work of reference which gives the gist of what is known about a great number of well-known remedies and medicinal agents.—*Pharm. J.*, 1914, vol. 92, p. 576.

*Useful Drugs.* (Editorial.)—"A Handbook of Useful Drugs," issued by the Council on Pharmacy and Chemistry of the American



Medical Association, is a selected list of important drugs suggested for the use of teachers of materia medica and therapeutics and to serve as a basis for the examination in therapeutics by State Medical Examining and Licensing Boards. The great aim of the compilation is to eliminate the mass of useless or superfluous drugs now in books on materia medica; it concerns products whose fixed value is generally recognized, and, therefore, it is particularly fitted to serve as a text on which teachers of materia medica and therapeutics may base their instruction. The properties, pharmacological action, therapeutic uses, and dosage of drugs are discussed concisely and in a practical manner. The methods of administration have received special attention, and there are occasional suggestions as to choice of a vehicle which will be of service to beginners in prescription writing. There is a table of solubilities of the medicaments in cold water and in cold alcohol, a pharmacological index, and a general index. The book may be studied profitably by the pharmacists and medical men of this country.—*Pharm. J.*, 1914, vol. 92, p. 278.

*Digest of Comments.*—A book review of Hygienic Laboratory Bulletin No. 87, including the Digest of Comments on the Pharmacopœia of the United States of America, and on the National Formulary, for the Calendar year 1911, says in part: "This volume is a rich source of references to articles in various journals and bulletins dealing in any way to the substances contained in the American Pharmacopœia, and places the user in position to readily find the original references in which he may be interested. The book is a model of compilation, such as one would expect from an international pharmacopœial secretariat."—*Pharm. Weekblad*, 1914, vol. 51, pp. 238, 239.

*The Era Formulary.*—Compilations of recipes for various objects and purposes have long been of interest to the retail druggist, and few stores in which the ordinary miscellaneous drug business is done can be profitably conducted without one or more books of this type. The new Era Formulary just published presents a collection of nearly 8000 formulas gathered from recognized authorities. The nine divisions of the volume include unofficial pharmaceutical preparations, toilet preparations, veterinary remedies, household remedies, paints, beverages, and miscellaneous preparations frequently called for by the customers of a live retail drug store. The material was compiled by William C. Alpers and Ezra J. Kennedy, and the book as published covers 521 large 8vo double-column pages, including an

index of 35 pages. As a compendium of suggestions for the up-to-date pharmacist this book should appeal to all pharmacists who are desirous of giving to their patrons the best possible service that they are capable of.

*Pharmaceutisch Weekblad*.—The number of this journal for April 3, 1914, concludes the fiftieth year of the publication and comprises 155 pages devoted to historical reviews of the progress of pharmacy during the past fifty years. As a supplement the publishers present a pamphlet of 98 pages, entitled "Monumenta Pharmaceutica," and containing a reprint of several historical papers of pharmaceutical interest. The first paper is a reprint of the communication by M. de la Condamine, "Sur l'Arbre du Quinquina," published in Paris in 1740. The pamphlet also contains a reprint of the paper by F. W. Sertürner (1817) in which he reports his discovery of morphine, a new base, and of meconic acid as being the principal constituents of opium. A paper by Smithson Tennant (1814) on the means of producing a double distillation by the same heat, a paper by John T. Barry (1819) on a new method of preparing pharmaceutical extracts, a paper by Thomas Thompson (1818) on Mr. Henry Tritton's patent for an improved apparatus for distillation, and a paper on the education of the apothecary, G. J. Mulder (1842), are also reprinted. This supplement is exceptionally interesting, in that it makes available for ready reference a number of the more important contributions to pharmaceutical literature.

*Acetyline* is a new name used in some portions of Europe for acetylsalicylic acid, and serves to further complicate the nomenclature of this now widely used substance.—*Pharm. Weekblad*, 1914, vol. 51, p. 578.

*Afridol* is described as sodium mercuri-o-toluylate, said to be an efficient substitute for corrosive mercuric chloride. *Afridol* is said to be active in dilutions up to 1:100,000, while corrosive sublimate is no longer active in solution of 1:50,000.—*Südd. Apoth.-Ztg.*, 1914, vol. 54, p. 62.

*Alypin*.—Lichtenstein, L., refers to the sudden fatal collapse after injection of alypin in a case reported by Proskauer and one by Ritter. Schröder and Garash have also reported cases of convulsions, stupor, and asphyxia after its use, and Lichtenstein adds another to this group.—*J. Am. M. Assoc.*, 1914, vol. 62, p. 975.

*Amorphous Phosphorus*. (*Anon.*)—A criticism on the introduction of amorphous phosphorus, a practically inert substance which is

being offered as a "valuable therapeutic agent."—*J. Am. M. Assoc.*, 1914, vol 62, pp. 793, 794. See also pp. 1033-1035.

*Argyrisms*.—Crispin, Antonio M., reports a case of argyrisms following the use of collargol. The administration of potassium iodide had not the slightest effect on the resulting color of the skin. The subsequent administration of hexamethylenamine caused the color to fade and become several shades lighter.—*J. Am. M. Assoc.*, 1914, vol. 62, p. 1394.

*Aspidospermine*. (Cow, Douglas.)—Experimental observations on the action of the alkaloids of quebracho. Quebrachine is by far the most toxic of the four alkaloids investigated. In small doses quebrachine exerts a stimulating action on the central nervous system, as also do the other alkaloids. The only obvious objective effect of this is seen in the respiration, which becomes both quicker and deeper.—*J. Pharmacol. and Exper. Therap.*, 1913-1914, vol. 5, pp. 341-356.

*Aspirin*. (Reed, Edward N.)—Report of a case of idiosyncrasy to aspirin (acetylsalicylic acid) in which vomiting, cyanosis, and œdema followed the ingestion of 5 grains of the drug. No treatment was instituted, and in about six hours the patient was comfortable.—*J. Am. M. Assoc.*, 1914, vol. 62, p. 773. See also p. 797.

*Creolin* consists of the glycerides of fatty acids along with cholesterolins, lecithin, and ethereal oil, all of which are found in yeast. It is prepared by extracting fresh purified beer yeast with alcohol and separating the dissolved fat from the alcoholic extract by suitable means. Creolin is said to be useful in furunculosis, acne, sycosis, and similar affections of the skin. It is also said to be useful in habitual constipation, leucorrhœa, erosions of the vagina and cervix, and similar diseases.—*J. Am. M. Assoc.*, 1914, vol. 62, p. 931.

*Cocaine*. (Editorial.)—The demand for cocaine for legitimate medicinal uses appears to have diminished considerably in recent years. Some of the large firms, which formerly handled many thousands of ounces of cocaine in the course of the year, now do not sell so many hundreds, while other firms which also dealt in the article in not inconsiderable quantities now sell practically none.—*Pharm. J.*, 1914, vol. 92, p. 466.

*Collargol*. (Eisendrath, Daniel E.)—A preliminary note on the effect of injecting collargol into the renal pelvis. The report states that death resulted in animals from extensive and widely-distributed collargol embolism, and the author believes that these experiments

offer for the first time a logical explanation of deaths observed in the human being.—*J. Am. M. Assoc.*, 1914, vol. 62, pp. 1392, 1393.

*Crotalin*.—Anderson, John F., reports a fatal case of bacterial infection from the use of the venom of *Crotalus horridus* dissolved in water. He also reports the examination of 95 ampoules of crotalin solution prepared by four different firms, 35 of which (38.8 per cent.) were found not to be sterile.—*J. Am. M. Assoc.*, 1914, vol. 62, pp. 893-895.

*Crotalin*. (Yawger, N. S.)—Report on six cases of epilepsy treated with crotalin. Two patients were uninfluenced; two were worse during the treatment; one early in the course developed such intolerant toxic symptoms that further experimentation was unjustified, and the last patient died two and a half months after treatment.—*J. Am. M. Assoc.*, 1914, vol. 62, pp. 1533-1535.

*Cymarín*.—A glucoside obtained from Canadian hemp, said to have an action on the circulation somewhat similar to digitalis and to be an efficient diuretic.—*Südd. Apoth.-Ztg.*, 1914, vol. 54, p. 62.

*Diachylon*. (Editorial.)—Newcastle-on-Tyne pharmacists have done one of the best things that we have heard of recently, by resolving to stop the sale of diachylon plaster in the lump, or any other form which may be taken internally. They have come to this resolution after hearing from Mr. T. Maltby Clague particulars of the cases of lead poisoning among women due to diachylon. Mr. Clague has had excellent opportunities in his investigations with Sir Thomas Oliver, M.D., of seeing the damage that is done by diachylon, and he considers that all self-respecting registered chemists should refuse to sell the stuff to anyone. Its legitimate use as a plaster is so trifling nowadays that the public would suffer little inconvenience if they could not buy it from pharmacies conducted under the act of 1908.—*Chem. and Drug.*, 1914, vol. 84, p. 458.

*Erepton* is a product prepared by the digestion of meat and consisting largely of amino-acids thus produced. It is prepared by the successive action of pepsin-hydrochloric acid, trypsin and erepsin on meat freed from fat and tendon; the end-product is then desiccated. Erepton is a brownish, hygroscopic powder, easily soluble in water and having an odor and taste suggestive of meat extract.—*J. Am. M. Assoc.*, 1914, vol. 62, p. 1559.

*Eusitin*.—Tablets containing the mucin substances obtained from *Althæa rosea syriens*. Intended for use in the treatment of obesity, the employment of those tablets being based upon their property of

abolishing the feeling of hunger from which patients suffer who are placed on a limited diet.—*Chem. and Drug.*, 1914, vol. 84, p. 443.

*Friedmann Remedy.* (Editorial.)—Several recent German articles on the Friedmann remedy appear to be uniformly unfavorable. They add to the testimony already given in this country that the Friedmann remedy is not inefficient alone, but also may be dangerous. All reliable reports regarding the treatment of patients by Friedmann's method seem to show either that it is actually injurious or else that it is less efficient than other well-known and less dangerous means of treatment.—*J. Am. M. Assoc.*, 1914, vol. 62, p. 1407. See also pp. 1206 and 1343.

*Hydrogen Peroxide.* (Stewart, R.)—There is really a very curious amount of ignorance prevalent as to hydrogen peroxide. The ordinary hydrogen peroxide of commerce is now an article sold by the ton, and even for many purposes of the drug trade this quality answers admirably. The ordinary commercial commodity, however, does not compare in stability with the higher-priced product used for medicinal purposes. The whole question is one of price. So long as drug stores, hospital authorities, and others expect a product at the very lowest possible price, it is hardly fair to expect manufacturers to deliver goods which it would cost two or three times the selling price to produce.—*Pharm. J.*, 1914, vol. 92, p. 353.

*The Hypophosphite Fallacy.* (Anon.)—A false therapeutic notion born of speculation soon dies a natural death if exposed unsupported to the cold world of facts, but when nursed by commercial interests it may be kept alive for generations. Interesting examples of this, to name but two or three, are the misconceptions perpetuated during the past half century concerning "lithia," the "natural" salicylates, and the hypophosphites. In spite of reliably reported observations, the hypophosphites continue to be employed by many practitioners, largely because the theory on which their use is based was thought to be plausible at the time when chemical theories were popular and gained a certain recognition and were adopted without scientific investigation. These theories were subsequently taken up by certain manufacturers and became a commercial asset, so that, as a result, a theory which uncommercialized would have died of inanition, was kept alive by continued advertisement.—*J. Am. M. Assoc.*, 1914, vol. 62, pp. 1346, 1347.

*Ipecacuanha.* (Van der Wielen and Reens.)—An assay of the same sample of ipecacuanha by the methods official in the Pharmac-

pœias named gave the following wide variation in results: Japanese Pharmacopœia, 1.78 per cent.; Belgian, 1.71 per cent.; United States, 1.67 per cent.; Swiss, 1.735 per cent.; Swedish, 1.735 per cent.; Austrian, 2.15 per cent.; Hungarian, 2.13 per cent.; Dutch, 2.06 per cent.; German, 1.54 per cent.; Italian, 2.03 per cent. These results point to the desirability of an international process and standard.—*Pharm. J.*, 1914, vol. 92, p. 541.

*Leukozon*.—Calcium perborate mixed with talc and standardized to a content of 5 per cent. of available oxygen. Used as an antiseptic dusting powder.—*Chem. and Drug.*, 1914, vol. 84, p. 443.

*Liquid Paraffin*.—Peck, J. Wicliffe, in discussing the production and use of liquid paraffin, says: "It has been stated that liquid paraffin should not be given with meals or during the process of digestion, as it prevents the pancreatic emulsification of fats. The experiments *in vitro* I do not think would be repeated in the body. From practical experience, just after a meal is the time I should suggest. If taken on an empty stomach the oil passes through very often unmixed with the stools and taking the usual thirty hours. When given in excess to animals it passes through with apparently no colorable fats dissolved."—*Pharm. J.*, 1914, vol. 92, p. 509.

*Novotryposafrol*.—A derivative of tryposafrol, for use in trypanosome infections and also in veterinary medicine.—*Chem. and Drug.*, 1914, vol. 84, p. 443.

*Perydal*.—An antiseptic dusting powder, containing formaldehyde and Peruvian balsam. It is used as a general antiseptic for wounds, for dusting in the stockings, and for infants.—*Pharm. J.*, 1914, vol. 92, p. 286.

*Phenolphthalein*. (Editorial).—A recent report of the laboratories of bacteriology and physiologic chemistry at the Jefferson Medical College in Philadelphia states that in twenty experiments, in each of which, before beginning the trials, the subject's urine showed no trace of albumin by delicate tests, 24-hour-specimen, collected after the administration of phenolphthalein in a from 1-grain to 2-grain dose, gave positive tests for protein in every case. The amount of albumin varied from a trace up to 0.25 per cent. by Esbach's quantitative method. The precipitate in many of the cases was tested and found to be insoluble in alcohol. Traces of phenolphthalein were demonstrated in the urine. The albuminuria lasted from one to three days.—*J. Am. M. Assoc.*, 1914, vol. 62, p. 1560.

*Phenolphthalein-agar* is agar-agar impregnated with phenolphthalein, 100 Gm. containing 3 Gm. of phenolphthalein. Phenolphtha-

lein-agar is prepared by impregnating 1000 Gm. of agar-agar with a solution obtained by dissolving 30 Gm. of phenolphthalein in a mixture of 2000 Cc. of water and 700 Cc. of alcohol and drying the impregnated agar-agar slowly.—*J. Am. M. Assoc.*, 1914, vol. 62, p. 1168.

*Quinine Poisoning.* (Underhill, Elizabeth C.)—Report of a case of quinine poisoning in a woman, age 20, who took at one dose 100 2-grain quinine pills. The toxic symptoms were accompanied by impairment of vision, which improved gradually.—*J. Am. M. Assoc.*, 1914, vol. 62, pp. 1396, 1397. See also p. 920.

*Quinine-urea Hydrochloride.* (Abstract.)—There is a certain element of danger attending the use of quinine-urea hydrochloride as a local anæsthetic. It has been pointed out that sloughing may follow its use when a solution stronger than 3 per cent. is used. An extensive abscess has followed the use of a 1 per cent. solution for the removal of internal hemorrhoids, and two cases of sloughing following the use of a 2 per cent. solution in similar operations are recorded. The general opinion is that solutions of this substance should not be stronger than 1 per cent.; some observers recommend even weaker solutions, and with proper attention to technic bad effects may be greatly reduced.—*Pharm. J.*, 1914, vol. 92, p. 368.

*Riopan.*—A concentrated preparation of ipecacuanha sent out as a brownish powder, soluble in water. It is standardized to contain 50 per cent. of ipecacuanha alkaloids in the form of their hydrochlorides; the other more or less inert substances are also present. One part of riopan is equivalent to 20 parts of ipecacuanha root.—*Chem. and Drug.*, 1914, vol. 84, p. 443.

*Salvarsan.*—No one can dispute the statement that many of the deaths from salvarsan have been caused by its ill-considered use, either in the face of contra-indications or in too large or too frequent dosage, but to argue from this that the fatalities are therefore not due to salvarsan and that salvarsan is not toxic is far from logical. The unwise use of salvarsan may be expected as a result of such arguments, and the stubborn denial of the toxicity of the drug has encouraged its careless administration.—*J. Am. M. Assoc.*, 1914, vol. 62, p. 1176.

*Neosalvarsan.* (Anon.)—Seven deaths have occurred in the Los Angeles Hospital within two days following intraspinal injections of a solution of neosalvarsan in autogenous serum, and another patient is reported as being likely to die.—*J. Am. M. Assoc.*, 1914, vol. 62, pp. 861, 862. See also pp. 957, 958.

*Sarsaparilla.* (Editorial.)—The proposition to include in the Pharmacopœia of the United States, Mexican, Honduras, Para, and Jamaica varieties of sarsaparilla is especially interesting in connection with the revision of the British Pharmacopœia, it being understood that this good old-fashioned drug does not commend itself to the Oxford Street savants, who desire to relegate it to the limbo of ex-official things.—*Chem. and Drug.*, 1914, vol. 84, p. 566.

*Serum Treatment of Tetanus.* (Editorial.)—The great value of antitetanus serum as a preventive is unquestioned. As a specific cure, however, this serum has fallen far short of the earliest expectations; it even has been asserted that so far the statistics and the evidence obtained from watching patients treated with serum do not indicate that it has any real curative value. It has been shown experimentally, however, that antitetanus serum may save animals already suffering from the symptoms of an otherwise fatal intoxication, but in order to accomplish this result the serum must be given in several hundred times the quantity required merely to protect, and it must be injected within a short time, from 24 to 36 hours, after the onset of the tetanus. Furthermore, it cannot be denied that the weight of statistics favors the serum.—*J. Am. M. Assoc.*, 1914, vol. 62, pp. 1174, 1175.

*Silver Methylene Blue* contains 24 per cent. of silver. Is being tried as an antiseptic, as it is assumed to possess a powerful bactericidal action in various infectious processes.—*Chem. and Drug.*, 1914, vol. 84, p. 443.

*Tenosin.*—The active constituents of ergot are now contracted to three substances, *p*-oxyphenylethylamine, beta-imidazolethylamine, and ergotoxin. For therapeutic purposes only the first two substances come into consideration, as the ergotoxin is the gengen-producing substance of ergot. Tenosin is said to be a mixture of the two amines mentioned above, and is available either in the form of ampoules or as a liquid for internal administration.—*Südd. Apoth.-Ztg.*, 1914, vol. 54, p. 63.

*Theobromine Sodium Salicylate.* (Puckner and Leach.)—Report of an investigation of the available brands of theobromine sodium salicylate. The results of the investigation, which are in the form of a table, show some variation in the moisture content and also in the actual theobromine content of the dried specimens; the variation is unimportant. The products in their original state (undried), as compared in relation to the theobromine content (the highest per-



centage of theobromine being 48.61, the lowest 45.24), reveal a variation of only about 3 per cent., a variation which is negligible in the case of such drugs as theobromine.—*J. Am. M. Assoc.*, 1914, vol. 62, pp. 1108, 1109.

*Tobacco Snuff.* (*Anon.*)—The Supreme Court of North Dakota holds constitutional the antisnuff act of that State of 1913, which makes it unlawful to import, manufacture, distribute, or give away snuff, or substitute therefor, under whatever name called.—*J. Am. M. Assoc.*, 1914, vol. 62, p. 1424.

*Tricarbin.*—Under this name, or as glycarbin, glyceryl carbonate has been introduced as a chemical inert diluent and basis for medicinal substances and galenical preparations such as pills, powders, tablets, and cosmetic preparations. It occurs as a crystalline non-hygroscopic, permanent, insoluble powder; it melts with decomposition at about 149° C.—*Pharm. J.*, 1914, vol. 92, p. 286.

*Vitamines.* (*Anon.*)—Vitamine is the name given to a substance which is believed to be necessary to prevent the nervous lesions characteristic of beriberi. It is regarded as an antineuritic agent naturally present in rice, the removal of which by polishing causes the symptoms of the disease to appear. The name appears to be derived from *vita* (life and amine), indicating its chemical character. The substance was at first thought to be a pyrimidine base with the following formula:  $C_{17}H_{20}O_7N_2$ . It was at first believed to have the constitution of a ureide, but in his latest work Funk states that the nitrogen is not present in the amino form. Vitamine was first found in rice and was connected with beriberi. Other substances of similar character were subsequently discovered, and the name has become descriptive of a class. Vitamine was discovered in 1912 by Casimir Funk.—*J. Am. M. Assoc.*, 1914, vol. 62, p. 1349.

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## CORRESPONDENCE.

AMENDMENT TO REGULATION 9, RELATING TO GUARANTIES BY WHOLESALERS,  
JOBBER, MANUFACTURERS, AND OTHER PARTIES RESIDING IN THE  
UNITED STATES TO PROTECT DEALERS FROM PROSECUTION.

Regulation 9 of the Rules and Regulations for the enforcement of the Food and Drugs Act, June 30, 1906 (34 Stat., 768), United States Department of Agriculture, is hereby amended, effective May 1, 1915, so as to read as follows:

## REGULATION 9. GUARANTY.

## (Section 9.)

(a) It having been determined that the legends "Guaranteed under the Food and Drugs Act, June 30, 1906," and "Guaranteed by (name of guarantor), under the Food and Drugs Act, June 30, 1906," borne on the labels or packages of food and drugs, accompanied by serial numbers given by the Secretary of Agriculture, are each misleading and deceptive, in that the public is induced by such legends and serial numbers to believe that the articles to which they relate have been examined and approved by the Government and that the Government guarantees that they comply with the law, the use of either legend, or any similar legend, on labels or packages should be discontinued. Inasmuch as the acceptance by the Secretary of Agriculture for filing of the guaranties of manufacturers and dealers and the giving by him of serial numbers thereto contribute to the deceptive character of legends on labels and packages, no guaranty in any form shall hereafter be filed with and no serial number shall hereafter be given to any guaranty by the Secretary of Agriculture. All guaranties now on file with the Secretary of Agriculture shall be stricken from the files, and the serial numbers assigned to such guaranties shall be canceled.

(b) The use on the label or package of any food or drug of any serial number required to be canceled by paragraph (a) of this regulation is prohibited.

(c) Any wholesaler, manufacturer, jobber, or other party residing in the United States may furnish to any dealer to whom he sells any article of food or drug a guaranty that such article is not adulterated or misbranded within the meaning of the Food and Drugs Act, June 30, 1906, as amended.

(d) Each guaranty to afford protection shall be signed by, and shall contain the name and address of, the wholesaler, manufacturer, jobber, dealer, or other party residing in the United States making the sale of the article or articles covered by it to the dealer, and shall be to the effect that such article or articles are not adulterated or misbranded within the meaning of the Federal Food and Drugs Act.

(e) Each guaranty in respect to any article or articles should be incorporated in or attached to the bill of sale, invoice, bill of lading, or other schedule, giving the names and quantities of the article or articles sold, and should not appear on the labels or packages.

(f) No dealer in food or drug products will be liable to prosecution if he can establish that the articles were sold under a guaranty given in compliance with this regulation.

W. G. McADOO,  
*Secretary of the Treasury.*

D. F. HOUSTON,  
*Secretary of Agriculture.*

WILLIAM C. REDFIELD,  
*Secretary of Commerce.*

WASHINGTON, D. C., May, 5, 1914.

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## ABOLITION OF GUARANTY LEGEND POSTPONED.

REVISED FOOD INSPECTION DECISION ALLOWS MANUFACTURERS ADDITIONAL  
YEAR IN WHICH TO EXHAUST STOCK OF LABELS.

WASHINGTON, D. C., May 29, 1914. It was announced to-day that it had been decided to postpone the effective date of Food Inspection Decision 153, which, in substance, abolishes, after May 1, 1915, the present guaranty legend on food and drugs.

This legend, now in general use by manufacturers, is "Guaranteed by (name of guarantor) under the Food and Drugs Act." The Secretaries of the Treasury, Agriculture, and Commerce have found it to be misleading and deceptive. Many people have been induced to believe that all articles labelled with the legend have been examined and approved by the Government. The facts are that putting the legend on labels by manufacturers is entirely voluntary, and that the Government never guarantees the wholesomeness or purity of food or drug products.

It appears that, acting in accordance with the regulation now in force, which permits the legend, many manufacturers have supplied themselves with large stocks of labels which cannot be used up by May 1, 1915. The result is that if the regulation, as amended by Food Inspection Decision 153, should go into effect May 1, 1915, large losses would accrue to citizens who have expended their money for labels in good faith and in an effort to comply with existing regulations.

To meet this situation the effective date of the amendment to the regulation will be postponed until May 1, 1916, and as to products packed and labelled prior to May 1, 1916, in compliance with law and with the present regulations, it will be postponed until November 1,

1916. Meanwhile, manufacturers may, and doubtless many will, label their good in compliance with the new regulations.

The decision is as follows:

FOOD INSPECTION DECISION NO. 155.

*Changing Effective Date of Food Inspection Decision No. 153, which Amends Regulation 9, Relating to Guaranties by Wholesalers, Jobbers, Manufacturers, and other Parties Residing in the United States to Protect Dealers from Prosecution.*

The effective date of Food Inspection Decision No. 153, issued May 5, 1914, is hereby postponed until May 1, 1916; *Provided*, That as to products packed and labelled prior to May 1, 1916, in accordance with law and with the regulations in force prior to May 5, 1914, it shall become effective November 1, 1916; *And Provided Further*, That compliance with the terms of Regulation 9 of the Rules and Regulations for the Enforcement of the Food and Drugs Act as amended by Food Inspection Decision No. 153 will be permitted at any time after the date of this decision.

C. S. HAMLIN,

*Acting Secretary of the Treasury.*

D. F. HOUSTON,

*Secretary of Agriculture.*

WM. C. REDFIELD,

*Secretary of Commerce.*

WASHINGTON, D. C., May 29, 1914.

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CURRENT LITERATURE.

CONSTITUENTS OF SENNA.

An investigation of senna leaves to determine the exact constituents present revealed many interesting things about this well-known drug.

Tinnevelly senna leaves (*Cassia angustifolia*, Vahl); senna leaves from Lima, Peru; which were found to be botanically identical with the Tinnevelly leaves, and Alexandrian senna leaves were used.

An alcoholic extract of the Tinnevelly leaves, when distilled with steam, yielded a small amount of an essential oil. From the portion of the extract which was soluble in water the following substances were isolated: Salicylic acid, rhein,  $C_{15}H_8O_6$ ; kaempferol,  $C_{15}H_{10}O_6$ ; aloe-emodin,  $C_{15}H_{10}O_5$ ; *kaempferin*,  $C_{27}H_{30}O_{16}$ ,  $6 H_2O$  (m. p.  $185^{\circ}$ – $195^{\circ}$ ), a new glucoside of kaempferol; a mixture of the glucosides

of rhein and aloë-emodin; the magnesium salt of an unidentified organic acid. The aqueous liquid furthermore contained a quantity of a sugar which yielded *d*-phenylglucosazone (m. p.  $216^{\circ}$ ), and some brown, amorphous products, which, on treatment with alkali, gave kaempferol, together with small amounts of rhein and aloë-emodin. Some amorphous, glucoside material was also present.

The portion of the alcoholic extract which was insoluble in water consisted of a soft, dark green resin, which amounted to 7.0 per cent. of the weight of the leaves employed. From this material, which contained considerable chlorophyll and amorphous products, there were isolated, in addition to some of the substances mentioned above, the following compounds: Myricyl alcohol; a phytosterol,  $C_{27}H_{46}O$ ; a phytosterolin,  $C_{33}H_{56}O_6$ ; palmitic and stearic acids.

The senna leaves from Lima, Peru, were found to contain all the above-mentioned compounds, with the exception of the magnesium salt, and, in addition, *isorhamnetin*. A glucoside of *isorhamnetin* was also present in association with glucosides of kaempferol, rhein, and aloë-emodin, but no pure compound could be isolated from the mixture.

Alexandrian senna leaves yielded, in addition to myricyl alcohol and a phytosterolin, rhein, aloë-emodin, kaempferol, and *isorhamnetin*. These four substances were also present in the form of glucosides, and in much greater proportion as such than in the free state.

The statements of Tschirch and Hiepe (*Arch. Pharm.*, 1900, 238, 427) that senna leaves contain "*sennaisoemodin*," "*sennachrysophanic acid*" (chrysophanol), and a "*substance,  $C_{14}H_{10}O_5$* ," could not be confirmed, it having been ascertained that the anthraquinone derivatives present consist solely of rhein and aloë-emodin. In this connection it may be noted that a mixture of approximately equal quantities of the last-mentioned two compounds has the empirical composition and properties assigned by Tschirch and Hiepe to the "*substance  $C_{14}H_{10}O_5$* ." Furthermore, the "*sennarhamnetin*" of the last-mentioned authors has been found to be identical with the *isorhamnetin* previously described by Perkin (*T.*, 1896, 69, 1658).

*Frank Tutin, from the Transactions of the Chemical Society, vol. 103, 1913. London.*  
J. K. T.

THE SERUM TREATMENT OF HAY FEVER.—In a pamphlet, by Lewis M. Somers, M.D., published by Fritzsche Brothers, New York, a summary of ten years' experience in the use of pollen

antitoxines, Dr. Somers demonstrates that from the very nature of the disease no single therapeutic agent can act as a specific, nor even modify the symptoms in every case. The serum formerly used was prepared by the action of the pollen toxin of either spring or fall plants upon the horse, and the resulting serum bodies being the therapeutic agent employed. Many experiments with the pollen toxin upon individuals subject to hay fever have shown that in dilutions of one in ten thousand, when placed in the eyes or nose, typical attacks of hay fever have been produced, in which the symptoms are as irregular and peculiar as in a natural attack. The use of the antitoxin in these artificial cases promptly checks the symptoms and causes the attack to disappear. In the case of individuals not subject to hay fever the toxin had no effect whatever. An antitoxin has been prepared by Dunbar, combining pollen from spring plants and fall grasses, and has been experimented with with satisfactory results. Summarizing the experience of ten years' use of pollen antitoxin, the following conclusions were reached: "1. The serum produces prompt and positive amelioration of the symptoms of hay fever in the majority of cases. 2. In a smaller number this is accompanied with complete disappearance of the affection for that particular season. 3. When results are obtained, it favorably influences all the manifestations of hay fever in the larger number of cases, while in a smaller class one or more of the symptoms seem to be most markedly influenced. 4. When given during the attack of hay fever, irrespective of its severity, it produces palliation rather than absolute cure. 5. When successfully used during one season, it does not prevent the reappearance of the disease the following season, although there is reason to believe that a slight influence in modifying further attacks does exist."

PHILIP F. FACKENTHALL.

#### THE U. S. PHARMACOPŒIA IX.

Prof. Joseph P. Remington, chairman of the Committee of Revision, in a recent address before the New York Branch of the A. Ph. A., stated that the work of revision was fast approaching completion and that the book would soon be printed. By international agreement it will contain the same strength and doses for all powerful preparations as do many of the leading pharmacopœias of the world. Tentatively, there will be 798 articles in the new U. S. P.

# THE AMERICAN JOURNAL OF PHARMACY

JULY, 1914

## CONTRIBUTION TO THE CHEMISTRY OF THE PITUITARY PRESSOR COMPOUNDS.

By ALBERT C. CRAWFORD and ZENO OSTENBERG,

From the Division of Pharmacology, Leland Stanford Jr. University.

After having discovered the pressor action of the extracts of the adrenal glands, Oliver and Schaefer<sup>1</sup> studied the action of those made from other ductless glands. They found that aqueous or glycerine extracts of sheep pituitaries, on intravenous injection into certain animals, caused a persistent rise in blood-pressure, usually, but not always, associated with a slowed heart-rate. This rise occurred even in animals with the medulla destroyed, and perfusion experiments proved the action to be mainly peripheral. An increase in the force of the heart action is partly responsible for this rise, as extracts of pituitary glands act directly on the muscle-fibres of the vessels and heart. The pressor action is especially marked in cases of artificially lowered blood-pressure.

The few experiments which Szymonowicz<sup>2</sup> made suggested that extracts of this organ caused a fall in blood-pressure with a rapid heart-beat, the opposite condition to what Oliver and Schaefer found. Silvestrini<sup>3</sup> merely noted a fall in blood-pressure, and this seemed to be the characteristic reaction. According to von Cyon, there are two compounds: one which slows and strengthens the

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<sup>1</sup> Oliver, G., and Schaefer, E. A., "On the Physiological Action of Extracts of Pituitary Body," *Jour. of Physiology*, vol. 18, p. 277 (1895).

<sup>2</sup> Szymonowicz, L., "Die Function der Nebennieren," *Archiv. f. Physiol.*, vol. 64, p. 131 (1896).

<sup>3</sup> Silvestrini, R., "Sull' azione dell' estratto aquoso del lobo posteriore dell' ipofisi sulla pressione sanguinea," *Revista critica di clin. med.*, No. 28, 1905, seen only in reference.

heart, while the other causes a rise in blood-pressure through inhibition of the depressor nerve.<sup>4</sup>

Howell<sup>5</sup> traced the pressor action of the pituitary exclusively to the infundibular portion, and found that, if the injection of extracts of this portion were repeated rapidly, the second injection caused no rise in blood-pressure and produced no cardiac inhibition. He also found that extracts of the anterior lobe usually induced no effect, either on the blood-pressure or on the heart-rate. If the vagi were intact, as in Oliver and Schaefer's original experiments, extracts of the infundibular lobe caused a rise in blood-pressure with a slow heart-beat, but if the vagi were cut there was a rise in pressure with less slowing than when the vagi were intact, hence the action is partly central. Other workers have found that some of the cardiac slowing is peripheral in origin.<sup>6</sup>

• In Howell's experiments both sheep and dog pituitaries were used and were tested on dogs. Schaefer and Vincent<sup>7</sup> confirmed Howell's conclusions that the pressor principle was confined to the infundibular portion, and the latter workers made the further suggestion that in extracts of this gland there was a depressor compound. They agreed with Howell that a second injection, if given too soon after the first, would cause no immediate rise in blood-pressure, but claimed there might be a delayed rise and that the second injection produced a more marked fall, so that no tolerance to the depressor action was produced. The depressor action still occurred after the use of atropin and was, therefore, not due to cholin. Slowing of the heart was not constant, but when present might be very persistent.

They found that the pressor compound, at least in the form in which it existed in the glands, was insoluble in alcohol or ether, while the depressor body was soluble in absolute alcohol. Schaefer

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<sup>4</sup> Cyon, E. v., "Die physiologischen Herzgiften," *Arch. f. ges. Physiol.*, vol. 73, p. 339 (1898).

<sup>5</sup> Howell, W. H., "Physiological Effects of Extracts of the Hypophysis," *Jour. Exper. Med.*, vol. 3, p. 245 (1898).

<sup>6</sup> Hebdorn, K., "Ueber die Einwirkung verschiedener Stoffe auf das isolierter Säugetierherz," *Skand. Arch. f. Physiol.*, vol. 8, p. 147 (1898); Cleg-horn, A., "Action of Animal Extracts . . . on Mammalian Heart Muscle," *Amer. Jour. Physiol.*, vol. 2, p. 273 (1899).

<sup>7</sup> Schaefer, E., and Vincent, S., "Physiological Effects of Extracts of the Pituitary Body," *Jour. Physiol.*, vol. 25, p. 87 (1899).



and Herring<sup>8</sup> found little or no rise in blood-pressure if the pituitary extracts were given animals by mouth, but believed the compound which gave immunity was still absorbed, because the depressor effect of intravenous injections was more marked if given after the oral use of such extracts. They state that a very small dose (1 c.c. of a 1 per cent. extract) does not produce immunity, although the rise in blood-pressure which follows a second injection is less than that which follows the first. In this connection it is interesting to note that Biedl<sup>9</sup> and also Cushing have found that removal of the posterior lobe is borne by dogs apparently with slight danger to life, whereas removal of the anterior lobe will cause death within a few days; also Ott and Scott<sup>10</sup> have found that the injection of extracts of the posterior lobe will cause a diminution in size of the thyroid gland, but that extracts of the anterior lobe will cause enlargement of this gland.

In Hamburger's experiments extracts of the anterior lobe caused a fall in blood-pressure with weakening of the heart and acceleration of the rate, while a second injection, if given early, produced no effect on the blood-pressure, although if the interval between injections was longer a fall still occurred. At the autopsy of one of Biedl's animals, similarly injected, there was widespread clotting.<sup>11</sup>

The fall from injection of extracts of the anterior lobe is more marked in atropinized animals, but Biedl<sup>12</sup> does not consider the fall produced by extracts of the anterior lobe as characteristic. Hamburger noted that a secondary rise at times followed the depression caused by the injection of extracts of the anterior lobe.<sup>13</sup>

Émile-Weil and Boyé<sup>14</sup> claim there is a further difference between the action of extracts of the anterior and of the posterior

<sup>8</sup> Shaefer, E., and Herring, P. T., "Action of Pituitary Extracts upon the Kidney," *Philos. Trans. Roy. Soc. London*, Ser. B, vol. 199, p. 1 (1908).

<sup>9</sup> Biedl, A., "Innere Sekretion," vol. 2, p. 116.

<sup>10</sup> Ott, I., and Scott, J. C., "Effect of Animal Extracts and Iodine upon the Volume of the Thyroid Gland," *Therap. Gaz.*, vol. 37, p. 781 (1913).

<sup>11</sup> Biedl, *l. c.*, p. 141.

<sup>12</sup> Biedl, *l. c.*, p. 141.

<sup>13</sup> Hamburger, W. W., "Action of Intravenous Injections of Glandular Extracts," *Amer. Jour. Physiol.*, vol. 11, p. 282 (1904).

<sup>14</sup> Émile-Weil, P., and Boyé, G., "Action différente des lobes hypophysaires sur la coagulation du sang," *Compt. rend. Heb. Soc. de Biol.*, vol. 67, p. 428 (1909).

lobes, in that extracts of the latter favor coagulation of the blood, while those of the former do not.

Paton and Watson<sup>15</sup> have found that extracts of the pituitary gland (pituitrin), when injected intravenously into birds, caused a fall in blood-pressure, and that after repeated injections this depressor action failed to appear, although, at times, such injections caused a rise in blood-pressure. In birds the fall in pressure was due to dilatation of the abdominal vessels, and might be neutralized by more powerful ventricular contraction.

It has been recently shown that the effects of extracts of the pituitary gland depend to some extent upon how rapidly they are injected; thus Miller and Miller<sup>16</sup> state that "if a strong saline extract of the posterior lobe of the hypophysis be injected rapidly a depressor effect only may be obtained, whilst if the injection be made slowly or in a very dilute form, the pressor effect predominates."

On purely histological evidence Herring<sup>17</sup> separated the pituitary gland into an anterior, a posterior, and an intermediary portion, and argued that the pressor principle originated in the pars intermedia. Recently Lewis, Miller and Matthews<sup>18</sup> have found that the more sharply the intermediary portion of the pituitary is removed and extracted, the greater the rise in blood-pressure which results from injection of such extracts, and the less of the pars intermedia is used the less the rise. Biedl claims that the pars intermedia can be removed comparatively easily in thyreoidectomized animals and that the injection of aqueous extracts of this portion of the gland causes a slowed heart with a rise in blood-pressure, while extracts of the pars nervosa, freed from the pars intermedia, are inactive, save in producing a slight fall.

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<sup>15</sup> Paton, D. H., and Watson, A., "Actions of Pituitrin, Adrenalin, and Barium on the Circulation of the Bird," *Jour. of Physiol.*, vol. 44, p. 413 (1912).

<sup>16</sup> Miller, J. L., and Miller, E. M., "Effects on Blood-pressure of Organ Extracts," *Jour. of Physiol.*, vol. 43, p. 242 (1911).

<sup>17</sup> Herring, P. T., "Histological Appearances of the Mammalian Pituitary Body," *Quart. Jour. Phys.*, vol. 1, p. 1214 (1908).

<sup>18</sup> Lewis, D., Miller, J. L., and Matthews, S. A., "Effects on Blood-pressure of Various Anatomical Components of the Hypophysis," *Archives of Int. Med.*, vol. 7, p. 785 (1911). See also Schickele, G., "Ueber die Herkunft der blutdrucksteigernden Substanz in der Hypophysis," *Zeits. f. gesam. Med.*, vol. 1, p. 545 (1913).

Lewis, Miller and Matthews believe the pars intermedia to be separated by the hypophyseal cleft into one portion closely connected with the anterior lobe and one with the posterior. This may explain why a rise in pressure may follow the injection of extracts of either lobe. They obtained a rise in pressure more frequently from injections of extracts of the anterior lobe than from those of the posterior. Schaefer and Herring were inclined to the view that the activity of the anterior lobe might really be due to postmortem infiltration.

Lewis, Miller and Matthews found that after removal of the depressor compound, extracts of the pars intermedia caused a rise in blood-pressure without slowing of the pulse-rate. They, like Howell, also noted that extracts of the posterior lobe caused a rise in blood-pressure, which was followed by a fall, and that there was then a return to the higher level. This fall after the primary rise was only seen when extracts of the posterior lobe were used, and they attributed this to a second depressor principle which was insoluble in alcohol.

Osborne and Vincent<sup>19</sup> found that the pituitaries of various teleostean fishes exerted a pressor action, and claimed that the central part of the infundibular portion of the ox pituitary had more pressor activity than the peripheral portion. In a recent comparative study of the pituitary gland Herring sums up the work as follows: "The presence of active physiological principles in the pituitary is associated with a tissue of nervous origin," and "there is reason to believe that the granules are the histological representatives of the active principles, and that they are the products of part of the epithelial lobe—the cells of the pars intermedia—carried to, elaborated in, and stored by, the pars nervosa."

Vincent and Sheen<sup>20</sup> took the position that pressor principles could be found not only in the pituitaries and suprarenals, but in greater or less extent in most tissues, and that boiling the extracts

<sup>19</sup> Osborne, W. A., and Vincent, S., "Contribution to the Study of the Pituitary Body," *Brit. Med. Jour.* (1900), vol. 1, p. 502.

<sup>20</sup> Vincent, S., and Sheen, W., "Effects of Intravascular Injections of Extracts of Animal Tissues," *Jour. of Physiol.*, vol. 29, p. 242 (1903). See also McCord, C. P., "Investigation of the Depressor Action of Pituitary Extracts," *Archives of Int. Med.*, vol. 8, p. 609 (1911); Berlin, E., "Hemocholin und Neosin," *Zeits. f. Biol.*, vol. 57, p. 1 (1911).

made from these organs usually enhanced the depressor action and masked the pressor effects. Miller and Miller found that, by autoclave treatment, the pressor action of pituitary extracts disappeared, while the depressor persisted.

It has been shown<sup>21</sup> that in cats the injection of extracts of pituitary glands, taken from almost any vertebrate animal, will increase the urinary secretion. This action has been claimed by some<sup>22</sup> to be due to its pressor principle, but there is physiological evidence to show that the diuretic and pressor actions are due to separate constituents. This diuretic action is confined to the posterior lobe, and second injections of such extracts do not produce tolerance to its diuretic effect, but rather increase its action. Extracts of pituitary glands taken from some animals have little or no effect on blood-pressure, yet exert a diuretic action.<sup>23</sup>

It has been found that extracts of pituitary glands exert an action on various organs which are supplied with unstriated muscles, such as the uterus,<sup>24</sup> intestines, bladder, etc. Recently Barger and Dale have shown that various amines will not only produce a rise in blood-pressure, but also affect various organs with unstriated muscles. In this case the action is on the extreme terminals (receptor bodies) of the sympathetic nerves supplying these organs, and these observers have designated this action as "sympathomimetic." In the case of the pituitary extracts the action, at least on the uterus, seems to be different, and is believed by Dale to be on the muscles rather than on the sympathetic nerve-endings. This view is supported by the experiments of Paton and Watson on birds.

The pressor principle and the one which causes uterine contractions may not necessarily be the same, or, at least, all of the uterine

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<sup>21</sup> Schaefer, E. A., and Herring, P. T., "Action of Pituitary Extracts upon the Kidney," *Philos. Trans. Roy. Soc. London*, Ser. B, vol. 199, p. 1 (1908).

<sup>22</sup> Houghton, E. M., and Merrill, C. H., "Diuretic Action of Adrenalin and the Active Principle of the Pituitary Body," *Jour. Amer. Med. Assoc.*, vol. 51, p. 1849 (1908).

<sup>23</sup> Herring, P. T., "Further Observations upon the Comparative Anatomy and Physiology of the Pituitary Body," *Quart. Jour. Exper. Physiol.*, vol. 6, p. 73 (1913).

<sup>24</sup> Bayer, G., and Peter, L., "Zur Kenntniss des Neurochemismus der Hypophyse," *Arch. f. exper. Path.*, vol. 64, p. 204 (1911).

action may not be due to the pressor principle. Engeland and Kutscher<sup>25</sup> have attempted to isolate the compound which causes contractions in the cat uterus. They attributed this action to cholin, as they isolated this base from pituitaries and found that control solutions of cholin caused contractions of the isolated uterus. Gautrelet had previously found cholin in the hypophysis. Engeland and Kutscher believe the pressor principle to be different from the one which acts on the uterus.

Bayer and Peter<sup>26</sup> claim that the pituitary principle which stimulates the autonomic nerve-endings of the intestines resides in the posterior lobe only and is not specific for this organ, and that the portion of the lobe insoluble in alcohol causes inhibition, while the portion soluble in alcohol causes increased activity. On isolated bronchial muscle, extracts of the hypophysis, histamine, and Witte's pepton caused no contraction.<sup>27</sup>

Like the secretion of the ovaries, extracts of the pituitary glands also increase the secretion of the mammary gland.<sup>28</sup> According to Herring,<sup>29</sup> extracts of the pituitary gland of skates produce an increase in mammary secretion, but do not produce a rise in blood-pressure or increase in urinary secretion.

The apparent similarity<sup>30</sup> in some of the actions of pituitary ex-

<sup>25</sup> Engeland, R., and Kutscher, F., "Ueber einige physiologischen wichtige Substanzen," *Zeits. f. Biol.*, vol. 57, p. 527 (1912); Schickele, G., "Ueber die Herkunft der blutdrucksteigernden Substanz in der Hypophysis," *Zeits. f. d. ges. exp. Med.*, vol. 1, p. 545 (1913); Bell, W. B., "Pituitary Body," *Brit. Med. Jour.* (1900), vol. 2, p. 1609.

<sup>26</sup> Bayer, G., and Peter, L., "Zur Kenntniss des Neurochemismus der Hypophyse," *Archiv. f. exper. Path.*, vol. 64, p. 204 (1911).

<sup>27</sup> Trendelenburg, P., "Physiologische und pharmakologische Untersuchungen an der isolierten bronchial Muskulatur," *Archiv. f. exper. Path.*, vol. 69, p. 106 (1912).

<sup>28</sup> Ott, I., and Scott, J. C., *Proc. Soc. Exper. Biol.*, vol. 1, p. 1911; Schaefer, E. A., "On the Effect of the Pituitary and Corpus Luteum Extracts on the Mammary Secretion in the Human Subject," *Quart. Jour. Exper. Physiol.*, vol. 6, p. 17 (1913); Gavin, W., "On the Effects of Administration of Extracts of Pituitary Body and Corpus Luteum to Milch Cows," *ibid.*, p. 13.

<sup>29</sup> Herring, P. T., "Contribution to the Comparative Physiology of the Pituitary Body," *Quart. Jour. Physiol.*, vol. 1, p. 261 (1908).

<sup>30</sup> Claude, H., and Baudoin, A., "Sur les effets de certains extraits hypophysaires," *Comp. rend. Acad. des Sci. Paris*, vol. 153, p. 1513 (1911); v. Frankl-Hochwart, L., and Fröhlich, A., "Zur Kenntniss der Wirkung des Hypophysins," *Archiv. f. exper. Path.*, vol. 63, p. 347 (1910).

tracts with those of epinephrin suggested the identity, or at least a close chemical relationship of the pressor principle of the pituitary with that of the adrenal glands, but Allers and Houssay <sup>31</sup> proved that the chemical reactions of pituitary pressor extracts were different from those of epinephrin, and the method used for isolating epinephrin from the suprarenal glands failed to yield this compound when tried on pituitary extracts. Meyers <sup>32</sup> has shown that, while repeated intravenous injections of epinephrin produced arterial degeneration in rabbits, pituitrin caused almost no vascular changes; and Cramer <sup>33</sup> has claimed that, while epinephrin when mixed with formaldehyde rapidly lost its pressor activity, Pituitrin when so treated retained this activity. Again, Meltzer <sup>34</sup> claims there is a difference in action on the enucleated eye between epinephrin and the commercial preparation of pituitary glands. Allers noted that Pituitrin, which is a dilute acetic extract of the glands, gave, like epinephrin, when treated with an alkali, an odor of an alkylamin. Fühner <sup>35</sup> has recently stated that B-iminazolyethylamine hydrochloride, or Histamin, when injected intravenously into rabbits, produces the same effects on blood-pressure and the respiration as Pituitrin, but admits it is not the active principle of the pituitary gland, as this substance is more toxic than a corresponding amount of Pituitrin, and while repeated injections of B-iminazolyethylamine will give some tolerance to the injections of the same, yet will not give immunity to Pituitrin, so that at one time Fühner suggested that the active principle of the pituitary gland is not B-iminazolyethylamine, but related to it. However, Einis <sup>36</sup> found that the action

<sup>31</sup> Allers, R., "Zur Kenntniss der wirksamen Substanz in der Hypophysis," *Münch. med. Woch.*, vol. 56, pt. 2, p. 1474 (1909); Houssay, B. A., "Estudios sobre la accion de los extractos hipofisiarios," p. 159.

<sup>32</sup> Meyers, M. K., "Die Wirkung von intravenösen Injektionen von Hypophysenextrakt," *Cent. d. Allg. Path.*, vol. 20, p. 109 (1909); Etienne and Parrisot, *Arch. de méd. Exper.*, July, 1908, found slight lesions.

<sup>33</sup> Cramer, W., "On the Inactivation of Adrenalin *in vitro* and *in vivo*," *Proc. Physiol. Soc.*, p. xxxvi; *Jour. of Physiol.*, vol. 42 (1911).

<sup>34</sup> Meltzer, S. J., "Influence of the Infundibular Portion of the Hypophysis upon the Pupil," *Proc. Soc. Exper. Biol.*, vol. 9, p. 103 (1912). See also Kepinow, p. 261.

<sup>35</sup> Fühner, H., "Das Pituitrin und seine wirksamen Bestandteile," *Münch. med. Woch.*, vol. 59, p. 852 (1912); Kaufmann, P., "Ueber den Einfluss der Organextrakte auf die Blutgefässe," *Zeit. f. Physiol.*, vol. 27, p. 532.

<sup>36</sup> Einis, W., "Ueber die Wirkung des Pituitrin und B-imidazolyethylamine auf die Herzaktion," *Biochem. Zeits.*, vol. 52, p. 96.

of B-iminazolyethylamine on the frog heart was different from that of Pituitrin. It is difficult to understand how this substance could be the active pressor constituent of the pituitary glands, because in carnivora it produces a fall in blood-pressure, although it produces a rise in pressure in herbivora, while pituitary extracts cause a rise in rabbits and dogs.<sup>37</sup>

Kepinow has pointed out a synergism between the action of epinephrin and pituitary extracts; that is, small doses of epinephrin are claimed to increase the action of pituitary extracts so that the combined action corresponds to more than their simple addition. Small inactive doses of extracts of the hypophysis increase the action of epinephrin on rabbits; in other words, the animal becomes sensitized.<sup>38</sup>

#### CHEMICAL EXPERIMENTS.

Considerable chemical work has been done on the pituitary glands, but apparently no pure pressor compound has as yet been definitely isolated. Calcium, phosphorus, bromine, arsenic, guanin, and cholin have been found to occur in the glands, and, while iodine was suspected, owing to an apparent histological resemblance between the thyreoid and pituitary glands, as yet it has not been proved to be present.

According to our experiments, repeated evaporation of extracts of the pituitary gland, and also putrefaction, will cause rapid diminution in pressor activity. Schaefer and Herring<sup>39</sup> noted that tryptic digestion for 18 hours did not destroy its diuretic or pressor action, and that peptic digestion, while it did not injure its diuretic action, changed the character of the pressor action.

Oliver and Schaefer found that aqueous extracts of pituitary glands could be boiled, at least for a short time, with little or no loss in pressor activity. Aldrich<sup>40</sup> extracted the fresh infundibular portion of the gland with dilute acetic acid and then removed the coag-

<sup>37</sup> Dale, H. H., and Laidlaw, P. P., "Physiological Action of B-iminazolyethylamine," *Jour. Physiol.*, vol. 41, p. 318 (1910-11).

<sup>38</sup> Kepinow, "Ueber den Synergismus von Hypophysis Extrakt und Adrenalin," *Arch. f. exper. Path.*, vol. 67, p. 247 (1912).

<sup>39</sup> Schaefer and Herring, *l. c.*, p. 22.

<sup>40</sup> Aldrich, T. B., "Preliminary Contribution to the Chemistry of the Infundibular Portion of the Pituitary Body," *Amer. Jour. Phys.* (1907-08), vol. 21, p. xxiii.

ulable proteins by means of heat and filtration. Aqueous extracts of undried pituitaries pass through filter paper with the greatest difficulty, but after thorough coagulation of the proteins the extracts filter readily.

As Lewis, Miller and Matthews showed that a pressor action could be obtained from all portions of the gland, we used the whole gland and avoided the tedious mechanical labor of removing the posterior portion. The fresh beef glands were ground in a meat-chopper and extracted twice with 0.1 per cent. acetic acid, and, after squeezing through cheese-cloth, the extract was coagulated on the water-bath and the filtrate evaporated *in vacuo*. This gradually colored during evaporation and left a brownish-yellow, gummy, non-crystalline mass, which, on intravenous injection into dogs, would induce a marked rise in blood-pressure.\*

On treatment with hot methyl alcohol (Merck's highest purity) all the color and activity went into the alcohol. This solution gave a heavy precipitate on the cautious addition of a drop or two of concentrated sulphuric acid, which redissolved with an excess of the acid. This precipitate dissolved in water, forming a reddish solution, and produced a marked rise in blood-pressure. When freshly precipitated it dissolved in hot methyl alcohol or ethyl alcohol (commercial 95 per cent.), but if washed with ether and placed in the desiccator became insoluble in either alcohol. At first we believed this to be a true sulphate mixed with calcium, but found that after further purification it failed to be reprecipitated from methyl alcohol by sulphuric acid, hence we argued that the first precipitation was merely mechanical. This precipitate, dissolved in water, or the acetic-acid extract of the glands, gave a heavy precipitate with lead acetate or lead subacetate, mercuric chloride or uranium acetate.

The filtrate after uranium acetate precipitation was active, but uranium gave no precipitate if the lead precipitation had been completely done. Mercuric chloride also gave a heavy precipitate and the filtrate was active. Gold chloride, platinum chloride, silver acetate, picric acid, picolinic acid, and benzoyl chloride with sodium hydrate, all gave precipitates with a solution of the sulphuric-

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\* NOTE.—These dogs were narcotized with ether and morphine and the vagi nerves were usually cut. The most satisfactory results were obtained by using young dogs. Older or large ones did not seem to respond well.



acid-alcohol precipitate, or from the acetic acid extract of the glands, but as yet we have been unable to obtain an active pressor compound from any of these precipitates. Aldrich claims to have obtained an active crystalline picrate by precipitation with picric acid from a concentrated solution of the glands purified by precipitation with uranium acetate, but he has published no analyses of this picrate.

We found that sodium tungstate gave an active precipitate which was soluble in acetic acid, but a control solution of sodium tungstate also caused a rise, hence we cannot say whether or not the activity was due to the reagent. We have been unable to throw out an active base by means of alkalies, or any active combination of it by means of aluminum hydroxide, but obtained an amine odor on treatment of active solutions with an alkali. Magnesium oxide seemed to carry down mechanically some of the pressor compound. No active volatile compound was obtained by alkaline distillation.

A marked odor of skatol arose on treating Pituitrin with hydrogen peroxide, and the solution lost its pressor action. Schaefer and Herring state that extracts of the pituitary glands, when treated with this reagent, still induced an increased urinary secretion, but produced merely a slight rise in blood-pressure. In their experiments reducing agents, such as zinc and hydrochloric acid, were without effect, either on the diuretic or on the pressor action of such preparations.

Recently Baudouin<sup>41</sup> claims that he has obtained an ash-free, hygroscopic compound by dissolving the dried acetic acid extract in absolute ethyl alcohol and freezing out the active substance. From methyl alcohol solution of the acetic acid extract we succeeded in freezing out, by means of solid carbon dioxide, an almost white precipitate which caused a marked rise in blood-pressure, and the filtrate was only slightly active, but on resolution of this active precipitate, freezing gave no precipitate.

After precipitating with lead subacetate and removing as much of the lead as possible by phosphoric or sulphuric acid the filtrate was still active, even though hydrogen sulphide was used to remove the last traces of lead; but if hydrogen sulphide alone was used to remove the lead, both the filtrate and precipitate became inactive, but solutions of the glands to which lead had not been added were

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<sup>41</sup> Baudouin, A., "Sur le recherche du principe actif de l'hypophyse," *Comp. rend. Soc. de Biol.*, vol. 74, p. 1138 (1913).

uninjured by hydrogen sulphide alone, hence the active pressor compound must have been carried down with the lead sulphide, but as yet we have been unable to recover it from the lead sulphide precipitate. From this precipitation and from the fact that it is completely removed or destroyed by animal charcoal we argued a high molecular weight, although this does not necessarily follow. After thorough precipitation with lead subacetate and freeing from lead with phosphoric acid the filtrate gave no biuret reaction, but gave a reaction with Folin's hydroxy-phenyl reagent. After lead-subacetate precipitation and removal of the lead, neither zinc sulphate nor ammonium sulphate (saturated solution) gave a precipitate.

In connection with one of our students we had begun some work with Caviar pepton\* and found that the intravenous injection into a dog of a few milligrams of it would produce a marked and persistent rise in blood-pressure. This at once suggested that there was a pepton which would cause a rise in blood-pressure, or that the rise which followed the injection of Caviar pepton was due to calcium or barium, supposedly used in neutralizing the acid used in the hydrolysis, or to amino-compounds arising in the formation of the pepton, or to albumose, or to some other unknown compound formed along with peptons.

We had noticed that an iodine and potassium iodide solution would produce a precipitate from certain pituitary extracts, and that this precipitate, after decomposing with sulphurous acid, was physiologically active, while Fühner has shown that various active principles were obtained from the phosphotungstic acid precipitate, and Aldrich has obtained an active principle by means of picric acid.

Now certain so-called peptons give precipitates with phosphotungstic acid, iodine and potassium iodide solution and picric acid, and produce an immunity, or rather a tolerance, to a second injection and interfere with coagulation of the blood. Pick and Spiro<sup>42</sup> showed that the depressor action on blood-pressure and the anti-coagulant action of Witte's pepton were not due to peptons or albumoses, but to some other compound associated with them; as Pick

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\* NOTE.—Supplied by the courtesy of the Hoffmann-La Roche Chemical Works of Grenzbach, Germany, through their New York branch.

<sup>42</sup> Pick, E., and Spiro, K., "Ueber gerinnungshemmende Agentien," *Zeits. f. Physiol. Chem.*, vol. 31, p. 235 (1900).

says, "Es gibt Peptone ohne Peptonwirkung und Peptonwirkung ohne Peptone." A number of so-called peptons produce eosinophilia in varying degrees. In some cases of acromegaly, a disease associated with pituitary disturbances, eosinophilia has been reported.<sup>42</sup>

Some pepton preparations induce symptoms similar to those which occur during the anaphylactic reaction. Biedl<sup>43a</sup> claims that Urechia's results with the intraperitoneal injections of pituitary extracts must be interpreted as an anaphylactic reaction, and Pan-kow<sup>44</sup> found that, after the intravenous injection of 1-5 c.c. of Pituitrin, rabbits became more sensitive to a second injection made in from 1 to 5 days after the first. According to Fühner, the respiratory stoppage from Pituitrin resembles that from anaphylaxis.<sup>45</sup> Extracts of the posterior lobe are said to accelerate coagulation of the blood, while those from the anterior lobe retard it.<sup>46</sup> Witte's pepton, especially the portion soluble in absolute alcohol, retards coagulation.<sup>47</sup>

The pituitary gland contains various enzymes, which might form pepton-like bodies.<sup>48</sup>

Paal,<sup>49</sup> by treating albumen with hydrochloric acid, has obtained products which he calls salts of pepton. These, unlike pepton, are soluble in alcohol. Schrötter<sup>50</sup> claims to have obtained similar compounds with albumoses. Peptons consist mainly of mono-amino acids, and, according to De Waele, the pepton action is primarily

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<sup>42</sup> Falta, W., "Die Erkrankungen der Blutdrüsen," 1913, p. 212.

<sup>43a</sup> Biedl, "Innere Sekretion," vol. 2, p. 133 (1913); Urechia, C. J., "Action de l'extrait hypophysaire en injections intrapéritonéales," *Comp. rend. Soc. de Biol.*, vol. 65, p. 278 (1908).

<sup>44</sup> Biedl, *l. c.*, vol. 2, p. 136.

<sup>45</sup> Fühner, *l. c.*, p. 406.

<sup>46</sup> Émile-Weil, P., and Boyé, G., "Action différentes des lobes hypophysaires sur la coagulation du sang," *Comp. rend. Soc. de Biol.*, vol. 67, p. 428 (1909).

<sup>47</sup> Zunz, E., "Apropos de l'action anticoagulante des injections intra-veineuses de peptone de Witte," *Comp. rend. Soc. de Biol.*, vol. 73, p. 50 (1912).

<sup>48</sup> Buetow, "Zur Kenntniss der Hypophysenzyme," *Biochem. Zeits.*, vol. 54, p. 40 (1913).

<sup>49</sup> Paal, C., "Ueber die Peptonzalze des Eieralbumine," *Ber. d. deutsch. chem. Gesells.*, vol. 27, p. 1845.

<sup>50</sup> Schrötter, *Monats. f. Chemis.*, vol. 14, p. 612 (1893).

an amino action. From Witte's pepton Pick<sup>51</sup> claims to have separated two peptons and four albumoses. However, as Haslam points out, the methods do not give sharp separations.<sup>52</sup> Pick precipitated the primary albumoses by means of ammonium sulphate, and separated them by alcohol; the hetero-albumoses<sup>53</sup> being precipitated by weak ethyl alcohol, while the proto-albumoses remained in solution with rather strong alcohol. The hetero-albumoses would precipitate on dialysis, and long heating converted them into an insoluble compound (dysalbumid). Witte's pepton contained very little of the proto-albumoses. After ammonium sulphate precipitation the filtrate yielded a product which was called albumose C. On treating the hetero-albumoses<sup>54</sup> with hydrochloric acid no tyrosin was obtained, but large amounts of leucin were found, while oxidation with potassium permanganate yielded a compound believed to be phenyl-amino-propionic acid. The proto-albumoses yielded tyrosin and gave a marked skatol odor on decomposition. Pick's hetero-albumose contained no indol nucleus, but yielded large amounts of di-amino compounds.

In one experiment Pick noted that both the proto-albumoses and hetero-albumoses obtained from Witte's pepton caused a rise in blood-pressure, but as these albumoses had been prepared by the ammonium sulphate method the rise may have been due to some of the precipitant. However, another dog merely responded by a fall in blood-pressure when hetero-albumose was injected, and in Popielski's experiments proto-albumose, prepared by Pick's method, produced a rise in blood-pressure in one case, but a fall in the second,<sup>55</sup>

<sup>51</sup> Pick, E. P., "Zur Kenntniss der peptischen Spaltungsprodukte des Fibrins," *Zeits. f. physiol. Chem.*, vol. 28, p. 219 (1899); *Beitrag z. Chem. Physiol.*, vol. 2, p. 481 (1902). See also Zunz, E., "Die fractionirte Abscheidung der peptischen Verdauungsprodukte mittelst Zinksulfat," *Zeits. f. physiol. Chem.*, vol. 27, p. 219 (1899).

<sup>52</sup> Haslam, H. C., "Separation of Proteins," *Jour. Physiol.*, vol. 36, p. 154 (1907-08).

<sup>53</sup> Kühne and Chittenden.

<sup>54</sup> Schulze, E., "Untersuchungen ueber die Amidosäuren welche bei der Zersetzung der Eiweissstoffe durch Salsäure und durch Barytwasser entstehen," *Zeits. f. physiol. Chem.*, vol. 9, p. 72.

<sup>55</sup> Popielski, L., "Ueber die Wirkungsweise des Chlorbaryum, Adrenalin und Pepton Witte auf den peripherischen vasomotorischen Apparat," *Archiv. f. exper. Path.*, Supplementband 1908, p. 441.

so that Popielski suspected barium to be present in one of the preparations.

Zunz<sup>56</sup> has also found that so-called hetero-albumose, thio-albumose, deuterio-albumose, and, especially, proto-albumose produced a rise in blood-pressure in dogs and rabbits. This rise was followed by a marked fall, but, in the case of the proto-albumoses, large amounts were necessary to produce the fall. Witte's pepton has been shown to exert both a vaso-constrictor and a vaso-dilator action.<sup>57</sup> Those products of digestion which gave no biuret test caused a marked fall in blood-pressure. These differences in results may really be due to a difference in the kind of proto-albumose or hetero-albumose used, as we have no positive proof that all fibrin from which Witte's pepton is obtained has necessarily the same chemical composition. Proto-albumose and syn-albumose caused recovery of the exhausted isolated heart, while peptons caused systolic stoppage.

Loeper and Esmonet<sup>58</sup> have found that a weak solution of what is called pepsin caused a slight fall in blood-pressure, followed by a rise. This rise was especially marked if the pepsin was treated with hydrochloric acid, and Popielski<sup>59</sup> noted that a hydrochloric acid preparation of the thymus gland would produce a rise in blood-pressure with a slowed heart, and, like pituitary preparations, produced this rise even after section of the spinal cord. This substance was not precipitated by phosphotungstic acid, lead acetate, or by platinum chloride in alcoholic solution, but was precipitated from absolute alcohol by an absolute alcoholic solution of mercuric chloride.

From this data we argued that some of the pressor activity was due to a compound with high molecular weight; that is, one closely allied to the proteins and which would not dialyse. Schaefer and Herring claimed that the pressor compound of the pituitary would

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<sup>56</sup> Zunz, E., "Untersuchungen ueber die Wirkung von Albumosen auf Blutdruck und Atmung," *Archives internat. de Physiol.*, vol. 11, p. 73; "Ueber die Wirkung von Albumosen auf das isolierte ueberlebende Schildkröten Herz," *Ibid.*, vol. 10, p. 290.

<sup>57</sup> Kaufmann, P., "Ueber die Wirkung des Witte-Peptones auf die Blutgefäße," *Zent. f. Physiol.*, vol. 27, p. 724 (1913).

<sup>58</sup> Loeper and Esmonet, "Action vaso-tonique comparée des different produite de sécrétion gastrique," *Comp. rend. Soc. de Biol.*, vol. 70, p. 8 (1911).

<sup>59</sup> Popielski, L., "Ueber eine neue blutdrucksteigernde Substanz des Organismus," *Zent. f. Physiol.*, vol. 23, p. 137 (1909).

dialyse, hence was not a protein. Using toluol as a preservative, we found that much of the color dialysed through heavy parchment paper,\* and that this colored solution was usually, though not always, active, while the liquid in the dialyser was intensely active. In this connection it may be remembered that Handovsky and Pick showed that there is in the serum a vaso-constrictor substance which is not dialysable<sup>60</sup> and which is not a globulin.

When our dialysate was collected in fractions, the last fractions were without activity, whereas the fluid within the dialyser was still very active, hence one of the pressor principles, perhaps the mother substance of the dialysable pressor principles, is non-dialysable. The depressor principle passes quickly into the dialysate.

After long dialysis the residue in the dialyser gives a slight precipitate with lead subacetate, none with mercuric acetate or a solution of iodine in potassium iodide, but gives a precipitate with phosphotungstic acid or phospho-molybdic acid and with stannous chloride or mercuric chloride. It also gives a strong biuret reaction.

Fühner claims to have separated from pituitary extracts by means of phosphotungstic acid precipitation and subsequent decomposition of the precipitate by means of barium hydrate various pressor compounds. On the other hand, Popielski claims that the pressor activity is in the phosphotungstic acid filtrate.<sup>61</sup> Now it has been found that phosphotungstic acid changes the chemical composition of various compounds,<sup>62</sup> hence there is a possibility that phosphotungstic acid would split our non-dialysable compound into various amines.

The active non-dialysable portion seems to correspond in some respects to the fraction separated by Raper under the name B $\alpha$ .<sup>63</sup>

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\* NOTE.—Animal membranes cannot be used for dialysis, as we have found that the pressor principles are completely removed from the solution by them and cannot be recovered.

<sup>60</sup> Handovsky, H., and Pick, E. P., "Ueber die Entstehung vasokonstriktorischen Substanzen durch Veränderung der Serummolloide," *Archiv. f. exper. Path.*, vol. 71, p. 62 (1913).

<sup>61</sup> Fühner, "Ueber die isolierten wirksamen Substanzen der Hypophysen," *Deutsch. med. Woch.*, vol. 39, p. 491 (1913); Popielski, L., "Hypophysis und ihre Präparate," *Berl. klin. Woch.*, vol. 50, p. 1156 (1913).

<sup>62</sup> Van Laer, H., "Nature of Amylase," *Bull. Acad. Roy. Belg.*, vol. 4, p. 13; quoted in *Chem. Abstr.*, vol. 8, p. 510 (1914).

<sup>63</sup> Raper, H. S., "Zur Kenntniss der Eiweiss-peptone," *Beitr. z. chem. Physiol.*, vol. 9, p. 168 (1907). See also Stookey, L. B., "Zur Kenntniss der Eiweisspeptone," *Beitr. z. chem. Physiol.*, vol. 7, p. 590 (1906).

## A NEW METHOD FOR THE DETERMINATION OF PHENOLPHTHALEIN.

By DR. A. MIRKIN, Cincinnati, O.

Since phenolphthalein has come into extensive use as an ingredient of laxative medicines, frequent occasions arise for its rapid and accurate determination. A few methods have been proposed, but, with the exception of one (*Pharm. Zentrbl.*, 1911, p. 1126), they are all gravimetical, therefore troublesome and unreliable, because applied to an organic substance.

In trying to find a volumetric method for its determination I took advantage of its property to form a well-defined oxime with hydroxylamine. This is the principle of Walker's method for carvone determination, and of Nelson and his estimation of a number of ketones, including camphor.

I first followed closely the directions worked out by the above-mentioned authors, but without result. I then worked according to Friedlander, who first discovered the phenolphthalein oxime, but the results were still far from satisfactory. Finally the following method was discovered, the results of which are very accurate:

1. Gramme phenolphthalein, 0.8 gramme hydroxylamine hydrochloride, and 0.52 gramme 90 per cent. sodium hydroxide solution, finely powdered, are dissolved in 35 to 40 c.c. of absolute alcohol and boiled for two to three hours under a reflex condenser until the liquid turns yellow. The liquid is then diluted with water, transferred to a 250 c.c. volumetric flask, 10 c.c. of 10 per cent.  $H_2SO_4$  are added and the flask filled to the mark with water. 50 C.c. are taken for titration. First the acid is neutralized, using Methyl orange as indicator. Then the excess of hydroxylamine is titrated with N/10 KOH, using phenolphthalein as indicator. A blank is run, using the same amounts of hydroxylamine, NaOH and alcohol, and boiled for the same length of time. The difference in the number of cubic centimetres of N/10 alkali used in the titration of the blank experiment and in the sample, multiplied by 316, gives the quantity of phenolphthalein.

When applying the method to medicinal tablets, the tablets were placed in a cylinder and crushed under alcohol with a glass rod. The alcohol was decanted off through a filter into a volumetric flask

and the extraction and decantation continued until complete extraction was obtained. An aliquot part of the extract was then taken for the determination.

The method gives very accurate results in the hands of a careful worker. The yellow color of the oxime does not interfere with the titration, as by proper dilution it colors the liquid only slightly.

Tablets of phenolphthalein frequently contain milk sugar or cane sugar, but as cane sugar does not give an oxime with hydroxylamine, and as milk sugar is practically insoluble in absolute alcohol, they do not interfere with the reaction. In case, however, that the method should give too high a result, it is better to make a volumetric determination of sugar in order to be more sure.

## THE ESTIMATION OF MORPHINE IN PILLS, TABLETS, ETC.\*

By J. B. WILLIAMS.

In a paper read before the last meeting of the Pharmaceutical section of the American Chemical Society Mr. A. D. Thorburn suggests the estimation of morphine in pills, tablets, etc., by making the aqueous solution alkaline and extracting with a mixture of phenyl-ethyl alcohol and benzene, partially evaporating the alkaloidal solution, extracting the residue with  $N/10$  acid and titrating back with  $N/10$  or  $N/50$  alkali, using hæmatoxylin as indicator. This method has recently been tried out with the following results. Duplicate assays of a 2 per cent. solution of morphine sulphate, using 10 c.c. (= 0.2 Gm. morphine sulphate or 0.1506 Gm. anhydrous morphine alkaloid).

$A = 0.1827$  Gm. morphine sulphate = 91.35 per cent.

$B = 0.1919$  Gm. morphine sulphate = 95.95 per cent.

The phenyl-ethyl alcohol mixture did not separate sharply even after standing two hours. The morphine is apparently not dissolved in the mixture, but appears to be held in suspension by it.  $N/50$  alkali was used in titration, but the end point with hæmatoxylin as indicator is not sharp or satisfactory.

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\* Presented at the meeting of the American Chemical Society at Washington, D. C., December, 1911.



Two further assays of the same solution were made, but after adding the phenyl-ethyl alcohol and benzene mixture and shaking, the separators were allowed to stand over night.

The morphine was precipitated through the liquid and on the sides of the separators. The crystals of morphine were washed off with alcohol and the assay completed. *A*, using cochineal as indicator, gave 0.1872 Gm. morphine sulphate = 93.6 per cent. *B*, with hæmatoxylin as indicator, gave 0.1805 Gm. morphine sulphate = 90.25 per cent. 2 c.c. N/10 acid and 4 or 5 drops of cochineal were added to *B* and again titrated, giving 0.1841 Gm. morphine sulphate = 92.05 per cent.

It was thought that perhaps by replacing the benzene in the phenyl-ethyl alcohol and benzene mixture with benzene or petroleum ether a sharper separation would be obtained. This was tried on a solution of 1 Gm. of morphine alkaloid and 50 c.c. N/10 acid in 100 c.c. Ten cubic centimetres of this solution titrated direct showed the presence of 0.0981 Gm. morphine alkaloid. Ten cubic centimetres extracted by the above modified method, replacing the benzene with petroleum ether, gave a sharp separation but low results, 0.08729 Gm. = 87.29 per cent. being obtained.

Judging from the limited number of assays made, the method is unsatisfactory both as to accuracy, time required, and cost and availability of material.

As above stated, the morphine does not seem to be dissolved in the phenyl-ethyl alcohol and benzene mixture—at least not in the quantity of solvent specified.

The U. S. P. gives the solubility of morphine in alcohol as 1-168 and in chloroform as 1-1800, but in a mixture of these two solvents it will dissolve far more freely than in either of them separately.

In order to ascertain the relative solubility of the freshly-precipitated alkaloid in these solvents, morphine sulphate was added in excess to alcohol, chloroform, and a mixture of alcohol 1 part and chloroform 2 parts, respectively. Sufficient ammonia was added to liberate the alkaloid, and the flasks shaken for two or three hours. Ten cubic centimetres of the filtered liquid were then evaporated to dryness and the alkaloid estimated volumetrically as crystalline morphine. The averages of several estimations, weight to volume, were as follows:

Solvent.	Wt. of cryst. morphine in 10 c.c.	Solubility w-v.
Alcohol .....	0.0547 Gm.....	1-182.6
Chloroform .....	0.0110 Gm.....	1-909
Alcohol 1 } .....	0.1316 Gm.....	1-76
Chloroform 2 }		

The solubility of precipitated morphine crystals (dried below 60° C.) in the same solvents was also determined, the average of a number of estimations being:

Solvent.	Wt. of cryst. morphine in 10 c.c.	Solubility w-v.
Alcohol .....	0.0421 Gm.....	1-237.5
Chloroform .....	0.0025 Gm.....	1-4000
Alcohol 1 } .....	0.1258 Gm.....	1-80
Chloroform 2 }		

Also the solubility of crystalline morphine in mixtures containing varying proportions of alcohol and chloroform:

Solvent.	Wt. of cryst. morphine in 10 c.c.	Solubility.
Alcohol 1 } .....	0.1324 Gm.....	1-75.5
Chloroform 1 }		
Alcohol 1 } .....	0.1258 Gm.....	1-80
Chloroform 2 }		
Alcohol 1 } .....	0.0879 Gm.....	1-114
Chloroform 4 }		
Alcohol 1 } .....	0.512 Gm.....	1-195.5
Chloroform 8 }		

Based on these experiments, the following assay method is recommended:

A number of pills or tablets, or a quantity of the sample for assay containing not more than 0.5 Gm. morphine (preferably from 0.1 to 0.2 Gm.), is dissolved in a few cubic centimetres of acidulated water, either in a separator or in a beaker, and then transferred to a separator, keeping the volume of the liquid as small as possible (from 5 to 10 c.c.); add from 15 to 25 c.c. of mixture of alcohol 1 part and chloroform 2 parts by volume and 2 or 3 c.c. of 10 per cent. solution of ammonia, or sufficient to make distinctly alkaline. Stopper the separator and shake well for 2 or 3 minutes. After separation, which usually takes place inside of a few minutes, draw off the chloroformic solution, filter through cotton, well wet with chloroform, into a wide-mouth flask or beaker of about 150 c.c. capacity. Repeat the extraction with two further like portions of

the alcohol chloroform mixture and then with three 10 c.c. portions of chloroform.

Evaporate the alcohol chloroform solution on a water-bath under a current of warm air to dryness, add a few cubic centimetres of alcohol and again evaporate. Dissolve the residue in an excess of  $N/10$  acid and titrate back with  $N/50$  alkali, using cochineal as indicator. Each cubic centimetre of acid neutralized by the alkaloid = 0.0301 Gm. of crystalline morphine or 0.0376 Gm. morphine sulphate.

Following are some of the results obtained by this method. A 2 per cent. solution of morphine alkaloid was prepared and assayed.

5 c.c. = 0.1 Gm. morphine gave.....	0.0976 Gm. = 97.6 per cent.
	0.0976 Gm. = 97.6 per cent.
10 c.c. = 0.2 Gm. morphine gave.....	0.1940 Gm. = 97.0 per cent.
	0.1952 Gm. = 97.59 per cent.
20 c.c. = 0.4 Gm. morphine gave.....	0.3901 Gm. = 97.52 per cent.
	0.3901 Gm. = 97.52 per cent.

A 2 per cent. solution of commercial morphine sulphate.

5 c.c. = 0.1 Gm. morphine sulphate gave....	0.09944 Gm. = 99.44 per cent.
	0.09944 Gm. = 99.44 per cent.
10 c.c. = 0.2 Gm. morphine sulphate gave....	0.1981 Gm. = 99.06 per cent.
	0.1981 Gm. = 99.06 per cent.
20 c.c. = 0.4 Gm. morphine sulphate gave....	0.3932 Gm. = 98.3 per cent.
	0.3940 Gm. = 98.5 per cent.

The quantity of solvent used in the extraction of this sample was the same in each case.

Two weighed quantities of another sample of morphine sulphate 0.0535 and 0.0560 Gm. gave 0.05395 and 0.05634 Gm. respectively when extracted.

A quantity of morphine alkaloid (1 Gm.) was dissolved in exactly 50 c.c.  $N/10$  acid, then made up to 100 c.c. with distilled water; of this solution two 10 c.c. portions were titrated and required for neutralization 8.7 c.c. and 8.7 c.c. of  $N/50$  alkali, showing the presence of 0.09813 Gm. of morphine in each. Two other 10 c.c. portions extracted by the above method, the residue dissolved in 5 c.c.  $N/10$  acid and titrated, required 8.7 c.c. and 8.8 c.c. of  $N/50$  alkali to neutralize, corresponding to 0.09813 Gm. and 0.09752 Gm. respectively.

Several other samples of morphine sulphate and morphine alkaloid gave equally good results. A large number of pills and tablets assayed by this method gave results approximating closely the theoretical content.

The advantages of this method are accuracy, simplicity, and shortness of time required for completion, duplicate assays being easily completed inside of two hours, except when, owing to the presence of sugar or gummy matter in the sample, slight emulsions may form, requiring a little more time for separation, although this can usually be prevented by keeping the aqueous portion to as small a volume as possible.

Since December, 1909, nearly one hundred assays by this method have been made by the writer and so far practically no trouble has been experienced. Of course, this method is available only where the morphine is not combined with other alkaloids, the identity of the alkaloid being taken for granted, but as a check on the manufacture of pills, tablets, etc., it has given good results.

A comparison of results obtained by the two methods follows.

10 C.C. OF A 2 PER CENT. SOLUTION MORPHINE SULPHATE.

*By Alcohol-chloroform Method.*

- I.....0.1984 Gm. morphine sulphate = 99.2 per cent.  
II .....0.1976 Gm. morphine sulphate = 98.8 per cent.

*By Phenyl-Ethyl Alcohol and Benzene Method.*

- A ..... = 0.1827 Gm. = 91.35 per cent.  
B ..... = 0.1919 Gm. = 95.95 per cent.

The solution containing 1 Gm. morphine alkaloid and 50 c.c. N/10 acid in 100 c.c. gave by direct titration 0.0981 Gm. morphine alkaloid in 10 c.c. and by extraction.

By alcohol-chloroform.		By phenyl-ethyl-alcohol & B. mod.
I.....	0.09812 Gm. = 98.12 per cent.....	} = 0.08729 Gm. = 87.29 per cent.
II.....	0.09752 Gm. = 97.52 per cent.....	

Time required for phenyl-ethyl alcohol method, 4 to 7 hours.

Time required for alcohol-chloroform method, 2 to 3 hours.

ANALYTICAL DEPARTMENT, PARKE, DAVIS & CO., DETROIT, Mich.

## BICHLORIDE OF MERCURY TABLETS AND BICHLORIDE TABLET LEGISLATION.<sup>1</sup>

By GEORGE M. BERINGER.

In presenting a paper on such a hackneyed subject as "Bichloride of Mercury Tablets and Bichloride Tablet Legislation," I am well aware that I may be trying your patience on a subject that you may perhaps consider as threadbare. My association with and study of this subject, however, convince me that this is not a dead subject, but contains several problems directly associated with the duties of the druggist and which pharmacists themselves, in a very large measure, must decide.

The extensive use of corrosive sublimate in this form has justified the decision of the Committee of Revision of the U. S. P. to introduce an official formula and by this means to endeavor to formulate additional safeguards to life in their use. The articles that have appeared in the medical, pharmaceutical and lay press, as well as the discussion in the committee, demonstrate that this is a live subject, and associated with it are several questions still to be settled.

In the official recognition of the tablet of mercuric chloride the U. S. P. is only following the example of most of the pharmacopœias that have been revised in recent years. A study of the foreign formulas and a comparison of these and likewise of the commonly used American formulas are interesting.

In American practice, either the Wilson formula containing a mixture of mercuric chloride and ammonium chloride or the Bernay formula containing mercuric chloride and citric acid has been almost exclusively used. In Europe the formula proposed by Angerer for *Pastilla Hydrargyri bichlorati* has been the type followed. His formula was:

Mercury bichloride,	
Sodium chloride, aa .....	0.5 Kg.
Eosin .....	1.0 Gm.

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<sup>1</sup> Read before the New Jersey Pharmaceutical Association, Lake Hopatcong, N. J., June 17, 1914.

Mix the salts and color the mixture with the eosin dissolved in water. Allow the mixture to dry in the air and compress into portions weighing 1 or 2 grammes each.

The German Pharmacopœia iv (1900), and again in the fifth edition (1910), adopts the title "*Pastilli Hydrargyri bichlorati*" and directs that from a mixture of equal parts of mercuric chloride and sodium chloride colored with a red coal-tar dye are to be made cylinders twice as long as thick and weighing 1 or 2 grammes each. Sublimate pastilles must be dispensed in sealed bottles labelled "*Poison*," and each pastille must be wrapped in black paper on which is printed in white the word "*Poison*" and the content of mercuric chloride stated in grammes.

The Swedish Pharmacopœia (1901), under the title of *Pastilli chlorati hydrargyrici*, directed that "*Sublimate pastilles*" should be hard cylinders or prisms weighing either 1 or 2 grammes each and composed of equal parts of mercuric chloride and sodium chloride and colored red by an aniline dye. It likewise introduced the requirement that each tablet must be wrapped in black paper on which was printed in white the word "*Poison*."

The Austrian Pharmacopœia (1906), under the title *Pastilli hydrargyri bichlorati corrosivi*, directed that equal parts of mercuric chloride and sodium chloride should be triturated to a thorough mixture and colored with a solution of eosin and compressed into pastilles weighing 2 grammes or 1 gramme. The pastilles are directed to be dispensed in glass bottles under a poison label, and the pastilles are to be singly wrapped in black paper with the word "*Poison*" imprinted in white.

The Swiss Pharmacopœia (1907) adopts as a title "*Hydrargyrum bichloratum compressum*," and as synonym "*Pastilli Sublimati*." The formula is mercuric chloride 666 Gm., sodium chloride 333 Gm., Eriocyanin A 1 Gm., mixed and compressed into tablets weighing 37.5 cg., 75 cg., and 1.5 Gm., and containing respectively each 25 cg., 50 cg., and 1 Gm. of corrosive sublimate. It directs that each tablet must be wrapped in black paper on which is printed in white the weight of the sublimate contained, the word "*Poison*," and a death-head design.

The British Pharmaceutical Codex, in the first edition of 1907, and likewise in the 1911 edition, gave formulas for a series of these tablets. Under the name of "*Solvellæ Hydrargyri Perchloridi*,"—Soluble Mercuric Chloride Tablets," and as a synonym "*Antiseptic*

Perchloride, or Corrosive Sublimate, Tablets," it directed a mixture of equal parts of mercuric chloride and sodium chloride colored with methyl violet to be compressed into tablets containing 8.75 grains of the mercuric chloride, so that one dissolved in the imperial pint (20 fl. ozs.) of water will make a 1/10 per cent. (1 in 1000) solution of mercuric chloride. Under the title "Solvellæ Hydrargyri Perchloridi Fortes or Strong Soluble Mercuric Chloride Tablets," a tablet of the same percentage of essential ingredients, but double the weight, was directed so that one dissolved in 20 fluidounces of water makes 1/5 per cent. (1 in 500) of mercuric chloride. Other formulas are given for a "mild" and for a "small" soluble mercuric chloride tablet yielding, when dissolved as directed, solutions 1 in 1000 and 1 in 4500, the latter being especially recommended as suitable for ophthalmic purposes.

The French Pharmacopœia (1908) presents a new style of formula for use of mercuric chloride in antiseptic solution. Its formula for Papier au Chlorure Mercurique or Charta hydrargyri bichlorati directs that 5 Gm. each of mercuric chloride and sodium chloride be dissolved in a sufficient quantity of distilled water to obtain a volume of 20 c.c. Filter-paper purified by treating with water containing one part of hydrochloric acid to the thousand, washing with pure water and drying, is then saturated with the mercuric chloride solution so that each rectangular surface 5 cm. by 10 cm. shall imbibe 1 c.c. of the solution and represent 25 cg. of mercuric chloride. The superscription, "Corrosive Sublimate" "twenty-five centigrammes," is directed to be printed with indigo carmine, thus producing, when immersed in the proper volume of water, a blue solution. The paper is to be protected from light and moisture and the container to be labelled in indelible red letters "POISON."

These specifications of the Pharmacopée Française, official in that country since July 17, 1908, will yield a product essentially the same as the corrosive sublimate leaflets now being made by an American manufacturer who claims originality and the right to a patent thereon as a new and novel invention.

The Italian Pharmacopœia (1909) gives the title "Pastiglie di Cloruro Mercurico" with the latin *Pastilli bichlorureti hydrargyri*. Its formula is mercuric chloride and sodium chloride equal parts colored with an aqueous solution of eosin and compressed into circular pastilles of 1 or 2 grammes in weight.

It is to be noted that most of the foreign pharmacopœias have simply followed in their titles that proposed by Angerer, and designate these tablets as pastilles. In the same pharmacopœias the title *pastilli* is frequently applied to mild remedial agents dispensed in the form of confections or lozenges. It is certainly an unfortunate designation and a dangerous classification that would include such a toxic form along with worm lozenges, cough troches, peppermint drops, etc. It is still more to be regretted that it has been proposed to adopt this same title in the U. S. P. IX. The use of the word "pastille" in this connection is not in accordance with the English usage of this word. As defined in the dictionaries the word "pastille" refers to several forms of substances of an entirely different character and dissimilar use.

The Century Dictionary defines *pastille* or *pastil*:

"1—A small roll of aromatic paste, composed of gum benzoin, sandalwood, spices, charcoal powder, etc., designed to be burned as a fumigator.

"2—A kind of sugared confection, usually of a strong flavor, of a round flat shape, like peppermint drops.

"3—In art: (a) a thin, round cake of water color; (b) the method of painting with water colors prepared as pastils or a drawing produced by them.

"4—In pyrotechny a paper case filled with a burning composition intended to cause rotation of a wheel."

Neither of these definitions would cover a mercuric chloride tablet of the shape described and the intended use. In medicine and pharmacy this title had already been preëmpted and used to a considerable extent for medicated confections, and its adoption for such a toxic official preparation is an exceedingly dangerous experiment. It was probably for this reason that the Pharmacopœia Helvetica adopted as its title "*Hydrargyrum bichloratum compressum*," and the British Pharmaceutical Codex "*Solvellæ*." The "*Solvellæ*" of the Codex are compressed tablets or discs intended to be dissolved in water for external or local use. The attempt at classification here made is a step in the right direction. The title coined, however, does not indicate the toxic character and, moreover, is subject to the criticism that it has the appearance of an attempt to imitate the trade-marked name of a certain brand of tablets extensively used in England.

The necessity is for a distinct title that will clearly differentiate



between the medicinal tablets used so extensively for oral administration and such poisonous tablets intended for external use. The safeguarding of life is the first and principal consideration, and this warrants the coining of a new title that shall distinguish the latter as a separate and distinct class. For this purpose I propose *Toxibellæ* as a distinctive class title, and as the official title for these tablets, "*Toxibellæ Hydrargyri Chloridi Corrosivi*," and as the English, "Poison Tablets of Corrosive Mercuric Chloride."

The foreign formulas follow the formula of Angerer in directing equal parts of mercuric chloride and sodium chloride. The American manufacturers generally claim on their labels to adhere to the Wilson formula. Tablets containing the proportion of ammonium chloride directed in this latter formula are prone to change on keeping. They deliquesce in humid atmospheres, and the solubility also deteriorates with age. For these reasons, some of the manufacturers have already substituted sodium chloride for part of the ammonium chloride. One manufacturer advises that he has found preferable a mixture of corrosive sublimate 7.3 parts, ammonium chloride 2.7 parts, sodium chloride 5 parts. The entire replacement of the ammonium chloride by the sodium chloride will doubtless yield a more stable and soluble tablet, and this change should be adopted in the pharmacopœial formula.

The coloring of bichloride of mercury antiseptic tablets was originally proposed not only to make them distinct in color from other tablets of the same shape and size, but the primal idea was to obtain a solution that would have a distinct color and not be mistaken and administered for harmless medications or water. Such accidents had occurred, and to prevent recurrence Angerer proposed as an additional safeguard that the solutions should be colored. It has been difficult to select a red dye that would possess sufficient tinctorial strength so that only a minute quantity would be required and at the same time be permanent and not altered by the action of the chemicals nor fade on keeping. This problem has confronted the manufacturers and has been the subject of considerable experimentation on the part of the writer.

Eosin in the quantity proposed yields a tablet that is distinctly pink, but when in solution (1 HgCl<sub>2</sub> in 1000) does not show a distinct color. This practical difficulty with the red dyes, their variable shades, and, moreover, the fact that confections are frequently of this color and liquid medicines are likewise commonly some shade

of red, have led to the use of other colors. The British Pharmaceutical Codex directs methyl violet, which in this combination gives a blue-purple solution. The Swiss Pharmacopœia orders Eriocyanin A, the sodium salt of a sulphonated dye of the triphenyl-methane-carbinol type that colors silk and wool a bright blue and is only slightly affected by 10 per cent. hydrochloric acid. The French Codex directs indigo carmine for this purpose.

A number of the manufacturers are already giving preference to the blue tablets. One of these writes: "Green and red colored tablets are not at all satisfactory. I believe that you will agree with me that a sombre blue would prove the most desirable. Confections are made in red, green, yellow, white, and every conceivable color, but the blue is not attractive and therefore would in all probability prove the safest. On the question of coloring for mercuric chloride, Dr. A. G. Rosengarten, whose firm prepares large quantities of mixed salts already colored for the manufacturers, writes me:

"The only satisfactory color that we have found is the blue dye, called indigo carmine. We have not yet found a satisfactory red or green dye, but I can highly recommend indigo carmine for consistent results, and a definite weight of that dye added to a definite weight of corrosive sublimate mixture will produce definite results. I cannot say the same about the other dyes, and I think it will be most desirable to confine the dyes for corrosive sublimate mixture to the one color, blue, and the one dye, indigo carmine."

My own experiments confirm these statements as to the availability of indigo carmine for this purpose. 2.5 mg. per tablet is sufficient to color 500 c.c. of water a distinct blue. If a more intense color be desired, this can be increased up to 5 mg., and the quantity to be specified in the formula for 100 tablets should not exceed .5 Gm. In my experiments with red dyes, iod-eosin and alizarin carmine (sodium alizarin sulphonate) appear to have given the best results with the Wilson type, but the color of the solutions is not as bright a red as might be desired. With the Bernay formula containing citric acid, methyl orange has shown the best results.

The official tablet should be adjusted to the basis of one tablet to 500 c.c. of water, yielding a 1 in 1000 solution, instead of one tablet to the pint, as has been the custom. This will necessitate only a slight increase in the weight.

The shape to be adopted for the official bichloride tablets is one of the questions that is being considered. When these tablets were introduced, the manufacturers quite naturally used the moulds that they had for their compressing machines, and so the unfortunate mistake was made of manufacturing these of the round or disc shape; the same shape and sizes as were used for innocuous medicinal tablets and confections. Fatal accidents have demonstrated that it is imperative that this dangerous practice should be discontinued. Toxic tablets of the bichloride of mercury antiseptic type should be made in a distinct shape that has not been used for any other purpose, and the use of such a shape or form should be restricted by legal enactments to such toxic tablets intended for external use.

In recent years the ingenuity of the American manufacturer has been exercised to obtain a distinctive shape that should characterize and distinguish his brand of "antiseptic tablets." As a result, we now have such shapes as triangular, diamond, square, cube, key-stone, clover leaf, exploited as proprietary forms of antiseptic tablets. Every one of these shapes has been commonly used in confections, and their official recognition and continuance for bichloride antiseptic medication would be a repetition of the original fatal error as to the shape of such tablets. The manufacturers of these shapes are each clamoring for the recognition of his particular shape.

The influence of these commercial interests has been exerted to prevent legislative action that would designate an appropriate shape or judicial consideration that would permit judgment to crystallize in favor of an official shape that would insure the greatest amount of protection to life. After all, the question of safety first is the paramount question.

Of all the proposals for a shape for bichloride of mercury tablets, the coffin shape suggested by Mr. F. M. Apple in his paper before the Pennsylvania Pharmaceutical Association seems to be best. This has already been adopted by at least four manufacturers, and its general adoption has only been prevented by the commercial interests back of other designs. Commercial instincts and financial advantages, and not the broad humanitarian principle of what is best to protect life, have been the causes actuating the opposition to legislation and to official recognition of the best suggestion yet offered.

The German Pharmacopœia has been quoted as an authority

to be followed in fixing the U. S. P. standard. I believe that we should appropriate from the foreign pharmacopœias all that our experience and judgment prove to be correct and in accordance with American practice. In this instance I cannot approve of following the dictum of the German Pharmacopœia. I have here a sample of the official German corrosive sublimate tablets that have been in my possession since last March. You will observe, first, that these are not uniform in color and that fading has commenced to take place. Secondly, the shape is in conformity with that of the Ph. Gr., twice as long as broad, and the manufacturer, to show this and possibly to permit of economy in using only half a tablet at a time, has made them with a ridge across the centre. This resembles forms of the pink linked phenolphthalein and other proprietary laxative wafers that are so extensively used in this country. It would be difficult to conceive of a more dangerous experiment than to officially recognize such a shape for bichloride tablets. It would be on a par with the adoption of the Italian pharmacopœial standard of the round tablet which we are now ready to condemn. There is no uniformity in the European pharmacopœias on this formula, and so the argument for adopting an international standard falls flat. Thirdly, the solution, when made of a strength of 1 to 1000, as commonly used, is so delicate a pink tint as to be barely perceptible.

So far as I know, no American manufacturer has yet placed on the market a bichloride of mercury tablet copied after that of the German Pharmacopœia. As this formula has been published for more than fourteen years, this is noteworthy and may be construed as an evidence of the good judgment of our manufacturers. To now insist that the U. S. Pharmacopœia must adopt and make legal a shape that has not met favor in American practice is a unique proposition that lacks the popular approval that is essential to its effectiveness.

The importance of throwing every safeguard possible around the sale and handling of such poisonous substances is now thoroughly recognized. The newspapers have given wide publicity to the deaths, either suicidal or accidental, occurring from bichloride tablets. The evils resulting from the overzealous newspaper which gives its readers all the details of the method by which some poor unfortunate has gone on the long voyage, have been discussed and decried, yet, nevertheless, it continues its course with little or no abatement.

A number of State legislatures in session during the past year have had under consideration acts that would restrict the handling of such poison tablets and define their shape, color, and label, and further prohibit the use of the prescribed shape for any other purpose. There are at least three bills on the same subject now pending in Congress. It is certain that we may expect legislation before long on this entire matter, and it is eminently proper that the drug trade should take an active interest in solving a question of public safety that is so closely associated with our business. Unfortunately, the attitude assumed by some of the druggists is that of thoughtless indifference. The argument advanced by others is that such legislation is only a passing sentimental fad and that it can have no influence on the protection of life. This is so fallacious that it can not long continue to prevent legislation.

It was never expected that any legislation would prevent a person of morbid mind from committing suicide. This is not the purpose of the proposed legislative enactments, but it is contended that in prescribing a distinctive shape for these poison tablets they could under no circumstances be mistaken, either in the day or night, for harmless medications. If a distinctive shape had been supplied the Macon, Ga., banker and the Brooklyn business man, whose deaths beyond question were accidental poisonings, at least these lives could have been spared.

The necessity for a distinctive shape for bichloride of mercury tablets is well shown by the compilation appearing in Public Health Report No. 46, by Martin I. Wilbert, of the United States Public Health Service. In this compilation Mr. Wilbert shows that at that time, in the current price-lists of five leading pharmaceutical manufacturers, there were sixteen different formulas and varying sizes of poison bichloride tablets, five different shapes, five different colors, and only three out of the sixteen were then made of any other shape than the ordinary round tablets used for medicine, such as headache and cold tablets. Could any stronger evidence of the necessity for restrictive legislation and a distinctive shape for these poison tablets be presented than this compilation in a Government bulletin, which shows the present dangerous and unsatisfactory method of marketing these tablets?

The influence of certain manufacturers on proposed legislation is shown in the act passed by the last session of the Maryland legislature. Instead of specifying in the act a distinctive shape or color,

the value of the legislation is largely nullified by the amended form in which the bill was passed. This law provides that "Tablets containing more than 1 to 10 grain of mercury bichloride must be of either triangular, diamond, square, oblong, or other irregular shape, and their color must be either blue, purple, or green, with the word 'Poison' imprinted or embossed on each tablet. Further, these tablets can only be sold, dispensed, or given away in bottles upon one side of which the word 'Poison' has been blown, and when a label with the word 'Poison' is placed on the face of the bottle."

The restrictions regarding the package and labelling are such as are commonly employed by all of the manufacturers, but the very needed protection to the consumer has been lost sight of by the overpowering commercial spirit that prevented the selection of a distinctive shape for the tablets. Any one of a number of shapes is equivalent to no shape, and the very indefiniteness of the act as passed through the influence of the manufacturers destroys its value as a measure for the safety of the public.

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## LIQUID PETROLATUM OR "RUSSIAN MINERAL OIL."

### REPORT OF THE COUNCIL ON PHARMACY AND CHEMISTRY.

The following report was submitted to the Council by a referee and publication authorized.

W. A. PUCKNER, *Secretary*.

Petroleum has been in use as a medicine from time immemorial. It was known to Herodotus 400 years before Christ, and is mentioned by Plutarch, Dioscorides, Pliny, and other early writers. It was extensively used by the Arabians and evidently played an important part in the practice of medicine in India, being known to the Bengalese as Muthe Katel. The raw product was the substance used in earlier times and differed much in character and composition, as obtained from different sources.

As an internal remedy it was early employed in chronic pulmonary affections, in obstinate skin diseases, in rheumatism, and for the expelling of tapeworms. It was extensively used for these several purposes in France under the name "Oleum Gabianum" and in North America as "Seneka oil." The internal use of the refined product may be traced to a patent granted to Robert A. Chesebrough,

of New York, in June, 1872, for the manufacture of a "new and useful product from petroleum, named vaseline." This name was originally applied only to a semisolid preparation, but later a liquid product known as liquid vaseline was marketed and for a time exploited as a cure for coughs, colds, consumption, and a number of other diseases and conditions.

The liquid petrolatum has since become known under a variety of names, proprietary and otherwise, in addition to being used as a substitute or an adulterant for other, more costly, fats and oils. Some of the names applied to the product are:

Adepsine oil	Neutralol
Amilee	Olo
Atoleine	Paraffin oil
Atolin	Paroline
Blandine	Petro
Crysmalin	Petrolax
Decline	Petrolia
Glyco	Petrolol
Glycoline	Petronol
Glymol	Petrosio
Heavy petroleum oil	Rock oil
Liquid albolene	Russian liquid petrolatum
Liquid cosmoline	Russian mineral oil
Liquid fossiline	Russian paraffin oil
Liquid geoline	Russol
Liquid paraffin	Saxol
Liquid petrolatum	Terralbolia
Liquid saxoline	Terraline
Liquid vaseline	Usoiline
Mineral glycerin	Water-white mineral oil
Mineral oil	White paraffin oil

A preparation similar to that official in the Pharmacopœia of the United States as liquid petrolatum has been included in many, if not all, of the foreign pharmacopœias, the official title under which this preparation is recognized being as follows:

Petrolatum liquidum, U. S. Pharmacopœia; Paraffinum liquidum, pharmacopœias of Great Britain, Germany, the Netherlands, Japan, Belgium, Austria, Denmark, Switzerland, Sweden, Servia, Italy, Hungary and Russia; Oleum Paraffinæ, Spanish Pharmacopœia; Vaselineum liquidum, French Pharmacopœia, and Oleum vaselini (as a synonym), pharmacopœias of Denmark and Russia.

The requirements of the several pharmacopœias differ somewhat, and the specific gravity as given is as follows:

U. S. P. VIII, 1905 .....	0.870 to 0.940 at 25°
Ph. Brit. IV, 1895 .....	0.885 to 0.890 at 15.5°
B. P. C. II, 1911, usually .....	0.875 or lower at 15°
Ph. Germ. V, 1910, at least .....	0.885 at 15°
Ph. Ross, VI, 1910 .....	0.880 to 0.885 at 15°
Ph. Hung. III, 1909 .....	0.88 to 0.89 at 15°
Ph. Ital. III, 1909 .....	0.875 to 0.890 at 15°
Ph. Fr. V, 1908, about .....	0.875 at 15°
Ph. Serb. II, 1908, about .....	0.880 at 15°
Ph. Svec. IX, 1908 .....	0.88 to 0.90 at 15°
Ph. Helv. IV, 1907 .....	0.880 to 0.885 at 15°
Ph. Dan. VII, 1907, at least .....	0.880 at 15°
Ph. Austr. VIII, 1906, at least .....	0.880 at 15°
Ph. Belg. III, 1906, not below .....	0.880 at 15°
Ph. Japon. III, 1906 .....	0.875 to 0.945 at 15°
Ph. Ndl. IV, 1905, not below .....	0.860 at 15°
Ph. Hisp. VII, 1905 .....	0.840 at 15°

For pharmaceutical purposes, liquid petrolatum may be divided into two grades, the lighter or more limpid oil, used extensively as a vehicle for oil sprays, and the heavier, more viscid oil generally recognized in European pharmacopœias and used as an ingredient of ointments and more recently as a remedy in the treatment of intestinal stasis.

Under petrolatum liquidum the U. S. P. recognizes a mixture of hydrocarbons, chiefly of the methane series, which occurs as a colorless or very slightly yellowish, oily, transparent liquid without odor or taste and having a specific gravity of about 0.870 to 0.940 at 25° C. For the U. S. P. IX, it is proposed to change this requirement somewhat so as to have it apply to a transparent liquid free from fluorescence, without odor or taste and having a specific gravity of from 0.845 to 0.940 at 25° C.

Such a requirement would include all of the available paraffin oils, irrespective of origin. The now commonly available commercial liquid petrolatum, used for pharmaceutical purposes, is practically colorless and all of the better grades are free from odor or taste. The specific gravity varies from 0.855 to 0.895. The lighter oils, having a specific gravity of from 0.860 to 0.870, are usually preferred in the making of oil sprays or solutions of substances to be used as



local applications. The product having a specific gravity above 0.875 evidently contains a considerable amount of dissolved solid paraffin which separates out at temperatures at or below 0° C., but readily dissolves again at temperatures above 10° C.

There is considerable difference in the chemical composition of the paraffin oils obtained from various sources. The American oil consists largely of hydrocarbons of the methane series, while the Russian oil contains naphthenes or hydrocarbons of the benzene series, having the empirical composition of ethylene ( $C_nH_{2n}$ ), which may be considered as hydrogenated aromatic hydrocarbons, though they behave with reagents very much in the same way as do the hydrocarbons of the methane series.

Mineral oils with a naphthene base are best suited for making white petrolatum, and at the present time the production of the colorless water-white liquid petrolatum appears to be confined largely or almost exclusively to the crude product of the Baku district of Russia, though it is asserted that it is now also made from the Hanover (Germany) crude oil and that some is being produced by "cracking" the white solid paraffin.

It is also said that the American oil can be made water white, but that it is not being so produced at present for economic reasons; the yellowish oil, free from fluorescence, having a very wide sale, both as a lubricant and as a substitute for lard oil and other of the more costly lubricating oils.

From a pharmaceutical point of view it would appear important to note the physical characteristics of the oil and to insist on absence of color, absence of odor and taste, absence of acid and of alkali and a specific gravity in harmony with the purposes for which the oil is to be used.

During the past year or two liquid petrolatum has attracted considerable attention as a remedy in the treatment of intestinal stasis or chronic constipation, the practice of using it having been developed largely through its recommendation by Sir W. Arbuthnot Lane and his associates. This use of liquid petrolatum and of petrolatum products generally is by no means novel. N. A. Randolph,<sup>1</sup> of Philadelphia, was among the first to suggest its use for this purpose in an article published in 1885. Randolph also ap-

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<sup>1</sup> Randolph, N. A.: *Therap. Gaz.*, 1885, ix, 732.

pears to have been the first to experiment with petrolatum and to determine its non-absorbability from the intestinal tract. In an article<sup>2</sup> in 1884 he concludes that "pure petrolatum while entirely unirritating to the digestive tract is valueless as a foodstuff."

The experiments recorded by Randolph were evidently prompted by the fact that vaseline and a number of imitation products then on the market were being sold as substitutes for lard and butter, and opinions regarding the food value of petroleum products appear to have differed very materially. Following the experiments of Randolph, Robert Hutchison in 1899 made a series of experiments to demonstrate that petroleum, petrolatum, paraffin and related products were absolutely unassailable by any of the digestive fluids, despite the "large vogue that had of late years been given to various petroleum emulsions, chiefly by ingenious and unterrified advertising." He came to practically the same conclusions arrived at by Randolph fifteen years earlier and pointed out that "liquid paraffin in one sense may be regarded as an artificial intestinal mucus and might in that way have some value on certain forms of constipation."

William Duffield Robinson<sup>3</sup> reports on the use of a perfectly refined colorless and odorless petrolatum, supposedly of American origin. He was able to show that all of the product passed unchanged through the intestinal tract and could be regained from the feces. In his conclusions he expressed the belief that the effect of the administration of these petroleum products is far more than as a simple intestinal lubricant. In over fifty selected cases in which nutrition, digestion and body-weight were impaired, and the purest oil administered in 1- or 2-dram doses each day for a period of from four to six months, there was in every instance an improvement of weight, health and feeling of well-being. The administration of refined paraffin oil gave no discomfort in any instance, even in cases in which nearly a pint was given in a few hours.

William Ewart<sup>4</sup> suggests liquid paraffin as a safe agent for the local treatment of the lesions in typhoid fever. He says in part: "Mineral oil, such as petrolatum or paraffin, is neither absorbed nor dissolved; therefore, after all absorbable ingestions are taken up by the lacteals, it will still remain in the bowel. In this way pure

<sup>2</sup> Randolph, N. A.: Proc. Acad. Nat. Sc., Philadelphia, 1884, p. 281.

<sup>3</sup> Robinson: William Duffield: *Med. News*, 1900, lxxvii, 56.

<sup>4</sup> Ewart, William: *Brit. Med. Jour.*, 1902, ii, 1505.

liquid paraffin is valuable, precisely because it is inert; moreover, it might some day, perhaps, be made the vehicle for effective topical remedies."

A. D. Schmidt<sup>5</sup> quotes Stubenrath as having given liquid paraffin in the treatment of chronic constipation, and he himself gave as much as 20 gm. of liquid paraffin to adults without observing any injurious effect whatever. He says, "As a result of the administration of liquid paraffin, the feces are softened considerably and are found under the microscope to contain numerous minute globules of paraffin." He was, however, unable to recover from the feces the entire quantity of paraffin administered and believes that a certain portion of it, probably the fractions with a low boiling-point, are absorbed or possibly oxidized in the organism.

Maurice Vejux Tyrode<sup>6</sup> also refers to the use of liquid petroleum in the treatment of constipation.

Sir F. Arbuthnot Lane in his recommendations of liquid petrolatum calls it an ideal remedy for stasis, but cautions against the use of the lighter oil as extensively prescribed in this country as a vehicle for sprays in nose and throat work.

Paraffin oil is not absorbed from the alimentary tract and so far as known exerts no deleterious influence. It is usually given in quantities of from 10 to 20 c.c. half an hour or an hour before meals or in larger doses, from 30 to 50 c.c., at one time on retiring. From available evidence it appears that comparatively huge doses may be administered without the production of any untoward results. According to many observers, liquid paraffin should not be given with or after meals because of the inhibiting influence that it may have on the digestion of food. It is not soluble in water or the ordinary solvents and therefore cannot be diluted. The denser oils are preferably slightly warmed or drunk with warm water so as to obviate the disagreeable slimy sensation that persists when taken cold.

Volatile oils may be used in moderate amounts to give a distinctive taste to the otherwise rather insipidly tasteless paraffin oil. Among the more desirable oils to be used for this purpose would be oil of peppermint, oil of cinnamon, oil of betula or methyl salicylate and oil of cloves. From 2 to 10 drops of any of these oils can be added to a pint of the oil. When larger doses of the oil are to be

<sup>5</sup> Schmidt, A. D.: *München. med. W'chenschr.*, 1905, lii, 1967.

<sup>6</sup> Tyrode, Maurice Vejux: *Boston Med. and Surg. Jour.*, 1910, clxii, 673.

given at one time, it would, of course, be advisable to use a comparatively smaller quantity of the volatile oil as a flavor.<sup>7</sup>

From the foregoing it would appear that apart from the Pharmacopœia of the United States, practically all other known pharmacopœias describe a water-white mineral oil under the title "Paraffinum Liquidum" or "Liquid Paraffin" as a colorless, odorless, tasteless, non-fluorescent, oily liquid, free from acids, alkalies and organic impurities. As explained before, the specific gravity of the preparation as recognized in other countries and as offered on the American market at the present time varies considerably, and there appears to be some difference of opinion as to the exact nature of the product that is preferable for use for different purposes. This matter requires further investigation.

Since the definition of liquid petrolatum in the U. S. Pharmacopœia permits the use of fluorescent products of widely varying specific gravities, it is recommended that physicians who desire the water-white non-fluorescent (Russian) mineral oil should use the term "Petrolatum Liquidum, Grave," or "Paraffinum Liquidum, B. P.," if the heavy product recommended by Lane is desired, and "Petrolatum Liquidum, Leve," if the light varieties are required. It is further recommended that under the foregoing names manufacturers and pharmacists be requested to dispense the products, in accordance with the following descriptions:

*Petrolatum Liquidum, Grave.*—Heavy (Russian) Liquid Petrolatum.—*Paraffinum Liquidum, B. P.*, liquid paraffin.—A transparent, colorless, tasteless, non-fluorescent, oily liquid, odorless when cold but giving off a faint petroleum odor on heating. This prepara-

<sup>7</sup> In addition to the articles referred to in the preceding footnotes, the following are of interest in connection with this subject:

Editorial, *Therap. Gaz.*, 1885, ix, 353.

Junker, F. A.: *Med. Record*, London, 1885, xiii, 506.

Editorial, *Med. News*, 1886, xlviii, 105.

Dunbar: *Deutsch. med. W'chenschr.*, 1896, xxii, 33.

Stubenrath, Franz Casimir: *München. med. W'chenschr.*, 1897, xlv, 639.

London Letter, *Med. News*, 1899, lxxiv, 504.

Hutchison, Robert: *Brit. Med. Jour.*, 1899, i, 724.

Schlesinger, E. G.: *Boston Med. and Surg. Jour.*, 1913, clxix, 14.

Lane, W. Arbuthnot: *Brit. Med. Jour.*, 1913, ii, 1126; *Proc. Roy. Soc.*

*Med.*, 1913, vi, 49; *Surg., Gynec. and Obst.*, 1913, xvi, No. 6.

Jordan, Alfred C.: *Practitioner*, London, February, 1913.

Chrysospathes, J. G.: *Zentralbl. f. Chir.*, 1913, No. 45; abstr., *The Journal A. M. A.*, Dec. 13, 1913, p. 2201.

tion should correspond to the requirements of the British Pharmacopœia for liquid paraffin and have a specific gravity of about 0.885 to 0.890 at 15° C. It is insoluble in water or alcohol, but soluble in boiling absolute alcohol and readily soluble in ether, chloroform, carbon disulphide, petroleum benzin, benzene, and fixed and volatile oils. It serves as a solvent for volatile oils and related substances like camphor, menthol and thymol.

This is the type of preparation used by Sir W. Arbuthnot Lane, and his associates for internal administration. It is also used as a basis for ointments and salves and as a local application to wounds, ulcers and in certain forms of skin diseases in which a simple protective is desired.

*Petrolatum Liquidum, Leve.*—Light (Russian) Liquid Petrolatum.—A transparent, colorless, tasteless, non-fluorescent, oily liquid, odorless when cold, but giving off a faint petroleum odor on heating. In other respects this preparation should correspond to the pharmacopœial tests for liquid petrolatum and have a specific gravity of about 0.860 to 0.875 at 15° C. Like the heavy variety of liquid petrolatum, it is insoluble in water and alcohol, but soluble in boiling absolute alcohol and readily soluble in ether, chloroform, carbon disulphide, petroleum benzin, benzene and fixed and volatile oils. It serves as a solvent for volatile oils and related substances like camphor, menthol and thymol.

This is a type of preparation extensively used as a vehicle for the oily sprays in nose and throat work. It is also being used as one of the constituents in the now popular paraffin oil cold cream and has been used to some extent for internal administration in the treatment of chronic stasis. Being more limpid than the preparation preferred by Lane, it is more readily taken, though greater care must be exercised in securing a sample devoid of the lighter fractions of petroleum distillates.

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## PHILADELPHIA COLLEGE OF PHARMACY.

### NINETY-THIRD ANNUAL COMMENCEMENT.

The commencement exercises on Thursday, June 18th, brought to a close one of the most successful commencement weeks in the history of the Philadelphia College of Pharmacy. A very large number of the alumni visited the college and attended the various functions. The Baccalaureate services were held at the Church of

St. Luke and the Epiphany, the Rev. David M. Steele delivering an unusually inspiring sermon. On Monday evening the Faculty gave their annual banquet to the graduating class in the College Auditorium. This is always a very interesting occasion, in that it brings together the Faculty and members of the graduating class in a very close relation, enabling them to discuss not only their experiences but some of the larger questions of life.

Tuesday was Alumni Day, the Association holding its annual meeting in the afternoon, and in the evening giving a reception to the members of the graduating class, in addition to the awards of the alumni prizes and a very excellent musical program. Prof. Henry Kraemer gave an address, in which he read the class oration which he had delivered twenty-five years ago, at the time of his graduation from this College. The annual alumni banquet, which was held at the Hotel Walton on Wednesday evening, was very largely attended and was characterized by magnificent alumni and college spirit. The responses by the various representatives of the classes ending in 4's and 9's showed that the movement to mark the centennial of the College and raise \$500,000 for new site, new buildings, and additional equipment would receive the hearty coöperation of the alumni.

The commencement on Thursday evening at the Academy of Music marked the climax of the week's celebration. The feature of the evening was the presence of the Governor of Pennsylvania, Hon. John K. Tener, who delivered a brief but very appropriate address to the members of the graduating class and their friends assembled. The opening prayer was made by Rev. W. Quay Rosselle, of Philadelphia, after which the degrees were conferred by President Howard B. French.

The title of Master in Pharmacy (Ph.M.)—In Course—was conferred on Professor Edwin L. Newcomb, P.D., of the University of Minnesota.

The following are the names of those receiving the degree of Doctor in Pharmacy (P.D.), together with the subjects of their graduating theses:

Name	Thesis
Ankrum, Samuel Martin.....	Acetone ..... Pennsylvania
Balliet, Woods D.....	Serums and Vaccines ..... Pennsylvania
Berryman, Clarence Haco.....	The Presence of Arsenic in Tin Foil ..... New Jersey

Name	Thesis
Biren, Samuel .....	Show Card Writing, Advertising and Displaying ..... Austria
Botdorf, Joseph Franklin ....	Kaolinum ..... Pennsylvania
Boyd, William Merton .....	Improved Methods of Preparing some U. S. P. and N. F. Preparations ..... Pennsylvania
Burke, John Joseph .....	Cork: Its Origin and Use ..... New Jersey
Cahan, Samuel.....	Sapo Mollis ..... Russia
Cameron, Ernest Clifford ....	Production of Cacao ..... Pennsylvania
Cantner, Paul Clifford .....	Acidum Hydriodicum Dilutum.. Pennsylvania
Carr, Edmund Eugene .....	Petroselin Fructus ..... Utah
Coble, Paul Daniel .....	Ammonium Hypophosphite..... Pennsylvania
Cohen, Louis .....	Pharmacy in Ireland ..... Pennsylvania
Collins, John Edmund .....	Sapo Mollis ex Oleo Gossypii Semiis ..... Pennsylvania
Comber, Gertrude Agnes [P.C.]	Magnesium Oxide ..... Pennsylvania
Coolbaugh, Leonard Ellsworth	Cudbear ..... New York
Craft, William Wheeler .....	The Typho-Bacterins ..... District of Columbia
Davidson, Wilmer Paul.....	Tincture of Iodine ..... Pennsylvania
Dickson, Thomas Young.....	Ground Flaxseed ..... Pennsylvania
Dils, Chauncey Lloyd .....	Manufacture of Window Glass.. Pennsylvania
Dougherty, Christ Patrick, Jr.	Aromatic Spirit of Ammonia.... Pennsylvania
Duvoisin, Agnes, [P.C.].....	Plasters and their Spreading... Pennsylvania
Edwards, Harold Powell.....	Elixir Ferri, Quininae et Strych- nine Phosphatum ..... Maine
Eldredge, William Payson....	Phenolsulphonaphthalein: Func- tional Test— ..... Pennsylvania
Epstein, Meyer Charles.....	Chocolate and Cocoa ..... Pennsylvania
Fiscel, John Arthur.....	Sapo Mollis ..... Pennsylvania
Fitzsimmons, William Henry..	Crude Petroleum ..... Pennsylvania
Flanagan, Clark Harrison....	Compound Syrup of Hypophos- phites, U. S. P. .... New York
Fox, James Andrew.....	Specifications for Portland Ce- ment ..... Pennsylvania
Frank, William Reuben.....	Incandescent Gas Lighting .... Pennsylvania
Fry, Daniel Joshua, Jr.....	Studies of the Origin and Tests of the True Oregon Balsam... Oregon
Gantert, Charles Louis.....	Mesquite Gum ..... Pennsylvania
Gehring, John Clucas.....	An Accounting System for the Average-Sized Drug Store.... Ohio
Gonya, Harry Herome.....	Calamine ..... Maine
Gray, John Calvin.....	Gentian ..... Pennsylvania
Greene, Barnett Russell .....	Hydrogen Peroxide, Production Past and Present ..... Pennsylvania
Griffin, William Harold.....	Theatrical Cold Cream ..... New York
Hagenman, Joseph Jeremiah..	Diluted Acetic Acid ..... Pennsylvania

## Name

## Thesis

Hall, Jasper Bonsall.....	Liquor Cresolis Compositus .....	Maryland
Harris, George Herbert.....	Paregoric .....	Pennsylvania
Hayes, John Harry.....	Modern Industrial Reducing Agents .....	New York
Heckenberger, William		
Welcome .....	The Three Cinnamons .....	Pennsylvania
Held, Ray Charles .....	Accurate Weighing .....	Pennsylvania
Helwig, George L. ....	Solution of Magnesium Citrate..	Pennsylvania
Hinman, Ralph Heber .....	Glycerophosphates .....	Pennsylvania
Hurley, William James .....	Syrup of Quinine .....	Pennsylvania
Johnson, Clarence Paul .....	Analysis of Viburnum Opulus...	Illinois
Johnson, Ernest Irvin .....	Medication of Zinc Stearate....	Maryland
Kahler, Frank Lot.....	Eucalyptus .....	Pennsylvania
Kauffman, Walter Melvin....	Structure of Viburnum Opulus and Various Viburnum Barks.	Pennsylvania
Kentch, Mortimer Adrian....	Medicated Baths and their Ex- temporaneous Preparation by the Pharmacist .....	Pennsylvania
Kinbach, Edwin Homer [P.C]	Glass Graduates .....	Pennsylvania
Kostenbauder, George Henry.	The Extemporaneous Preparation of Medical Bougies .....	Pennsylvania
Krick, Harry Nunemaker....	Elixir Terpini Hydratis .....	Pennsylvania
Kulp, Jacob Harold.....	The Evils of Newspaper Prescrib- ing .....	Pennsylvania
LaCourse, Anthony, Jr.....	Silicon Carbide .....	New York
LaWall, Edgar Sciple.....	Carbon Dioxide in Atmospheric Air and Its Estimation.....	Pennsylvania
Leidich, Stewart Grier.....	The Cultivation and Handling of Golden Seal .....	Pennsylvania
Leinbach, Allen Abraham....	Purity of Commercial Gelatin...	Pennsylvania
Llewellyn, Walter Palmer....	Bermuda Arrowroot .....	Bermuda
Lodge, Roy Paul .....	The Electrolytic Manufacture of Organic Compounds and Fine Chemicals .....	New Jersey
McCall, Enzer Lewis .....	Clay .....	Pennsylvania
McKean, Harold Andrew [P.C]	The Salt Industry in New York State .....	New York
McLarren, Chester Lee .....	Piscidia Erythrina .....	Pennsylvania
Marshall, Forrest Scott.....	Tea and Its Caffeine Yield....	Pennsylvania
Merz, Elmer Frank .....	The Phosphates of Calcium ....	Pennsylvania
Morehead, Robert Crosier...	Burgundy Pitch .....	Virginia
Murtoff, Robert Goulden....	Acetylene .....	Pennsylvania
Myers, Nervin Amos.....	Bacterins .....	Pennsylvania
O'Hare, Charles Vincent.....	Oleum Amygdalæ Amaræ et Benzaldehydum .....	Kentucky
Owings, Irl Washington.....	Tablet Making in the Retail Drug Store .....	Ohio



Name

Thesis

Pettit, Roland Levi.....	Face Creams .....	New Jersey
Rachmell, Nathan.....	Cottonseed .....	Pennsylvania
Rogers, Ralph Benjamin.....	Acacia .....	New Jersey
Rosenberg, Julius Jacob .....	Cork .....	New York
Rosoff, Maurice .....	Drug Standardization and Its Value in Pharmaceutical Prep- arations .....	Pennsylvania
Rowland, Norris Dean.....	Colorimetric Test for Cubeb.....	Pennsylvania
Russell, Charles Allen.....	Potassa Sulphurata .....	Pennsylvania
Salsbury, Venola Bruce.....	Emulsion of Cod Liver Oil .....	Pennsylvania
Schadt, Ralph Monroe.....	Insecticides .....	Pennsylvania
Semmel, Irvin Clarence.....	Prescription Precipitation .....	Pennsylvania
Shover, Raymond Leslie.....	Assay of Donovan's Solution....	Pennsylvania
Shumaker, Henry Ward.....	Hygienic Laboratory of the U. S. P. H. Service .....	Pennsylvania
Slipakoff, Isadore .....	Sponges .....	Pennsylvania
Spangler, Edwin Royer.....	The Rhizome of Asarum Cana- dense .....	Pennsylvania
Steever, Ernest Leo.....	Maple Sap, Syrup and Sugar....	Pennsylvania
Stines, George Findley.....	Carum .....	Ohio
Sutton, Stanley Eugene.....	Colloids, their Chemistry and their Practical and Thera- peutical Applications .....	New Jersey
Taylor, Leander Gifford, Jr. ..	Physiologic Saline Solution .....	New Jersey
Taylor, William Henry.....	Logwood .....	Pennsylvania
Thompson, Frank Davenport..	Peroxides and Perborates. ....	Pennsylvania
Train, Earl Fred.....	Manna .....	New York
Trambley, Leo Thomas.....	The Chemistry of Paper Making.	Pennsylvania
Veigel, Charles Joseph .....	Volumetric Estimation of Mer- cury .....	Pennsylvania
Waker, James Schuteman....	Aromatic Fluidextract of Cas- cara .....	New Jersey
Watson, John Russell....	Camphor: Natural and Synthetic	Pennsylvania
Watson, Walter Irving.....	Urinalysis .....	Rhode Island
Way, John Cloud, Jr. ....	The Contributions of Ancient Greece to Modern Medicine....	Pennsylvania
Weinstein, Abram.....	Hirudo .....	Pennsylvania
Wheeler, Elwyn J.....	Certified Food Colors .....	N. Hampshire
Whipple, Oscar Kellog, Jr.,...	Weeds Used in Official Pharmacy	New Jersey
White, Charles Albert, Jr., [P.C.] .....	Bee Culture and Its Products Used in Pharmacy .....	New Jersey
Willmers, Horace William....	Sandalwood .....	Iowa
Wolverton, Fred Cleveland...	Podophyllum: Fruit and Its Ad- juvant Syrup .....	Ohio
Wyman, Abraham .....	Sodium Chloride .....	Pennsylvania

The following are the names of those graduates who received the degree of Pharmaceutical Chemist [P.C.], together with the subjects of their theses:

Name	Thesis
Flack, George Thomas	Unfermented Grape Juice, Manufacture and Use ..... Pennsylvania
Flottman, Charles August	Monazite Sand ..... Pennsylvania
Hansell, Henry Lewis	Compound Syrup of Hypophosphites (Cloudy) ..... Pennsylvania
Heinle, Charles Jacob	Paper ..... Pennsylvania
Hogstad, Anton, Jr.	Belladonna ..... Wisconsin
Kutteroff, Charles Frederick	Camphor and Its Preparations ... New Jersey
Porter, Clarence Frank Turner	Methods for Recovering Volatile and Fixed Oils from Emulsions Tennessee
Quin, John Frederick Gartner	The Production of Cottonseed Oil ..... Pennsylvania
Schoonover, Harold Nelson	Buttermilk Cold Cream ..... Pennsylvania
Wallace, William Romine	The Constituents and Manufacture of Fertilizers ..... Pennsylvania
Webb, Alvin Chester	Gallæ ex Rhus glabra ..... New Jersey

Certificates of Proficiency in Chemistry were awarded the following:

Bush, John Lyol	Pennsylvania
Cowles, Henry Carleton, Jr.	Pennsylvania
Hinski, Herman Leo [P.D.]	Pennsylvania
Karns, Harry Clifford, Jr. [P.D.]	Pennsylvania
Kind, Paul Adolph	New Jersey
Tucker, George W.	Pennsylvania

Certificate of Proficiency in the Food and Drug Course:

Clark, Roy Lavender	Utah
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Certificates in Bacteriology were awarded the following:

Aguizy, Ahmed Mahmoud El	Egypt
Atkins, John Walter [P.D.]	Pennsylvania
Brown, West Smith [P.D.]	Pennsylvania
Garrett, Joseph Jeffreys	Florida
Hite, Earle Milton	Pennsylvania
Huber, Donald Witherow [P.D.]	Pennsylvania
King, James David [P.D.]	Pennsylvania
Kulp, Jacob Harold	Pennsylvania
Grauss, Gustave Adolph, Jr.	New York
Leathers, Fred. S.	New York
Lemon, Allan	Michigan
Loehle, Frank Aloysius	New York

Linford, Louis George .....	New York
Merner, Paul Marcus Pfeiffer .....	Iowa
Patterson, Donald Malcolm .....	New Jersey
Potterfield, Garland Blair .....	West Virginia
Sands, Paul Douglass [P.D.] .....	Pennsylvania
Shumaker, Henry Ward .....	Pennsylvania
Smith, John Preston .....	Pennsylvania
Spangler, Edwin Royer .....	Pennsylvania
Starr, Miss Mabel .....	Connecticut
Stein, Joseph .....	Pennsylvania
Wallace, William Romine .....	Pennsylvania

#### AWARD OF PRIZES.

The Martin Cup, awarded to the graduation class obtaining a higher average than the one immediately preceding it, was awarded to the class of 1914 and accepted on behalf of the class by their president, Elwyn J. Wheeler, the presentation being made by President French.

The Welcome Cup, awarded to the second year class attaining a higher general average than the preceding class holding it, was awarded to the class of 1915, and was accepted on behalf of the second year class by their president, William R. Tenney, the presentation being made by President French.

"The Graduate 1913" Cup, awarded to the Freshman class for high general record in scholarship, and to be competed for by succeeding Freshman classes, was for the first time presented to the Freshman class of this year and accepted on behalf of the class by their president, Harvey V. Stokely, the presentation being made by Joseph F. Elward, P.D., of the class of 1913.

The grade of distinguished was obtained by Stanley E. Sutton. The following attained the grade of meritorious: W. D. Balliet, L. Cohen, E. S. LaWall, W. R. Wallace, A. C. Webb, A. Weinstein.

The William B. Webb Memorial Prize, a gold medal and certificate, offered for the highest general average in the branches of Committee, Operative Pharmacy and Specimens, was awarded to Stanley E. Sutton, the presentation being made by Joseph L. Lemberger.

The Chemistry Prize, \$25, offered by Prof. Samuel P. Sadtler, for knowledge of Quantitative Chemical Analysis, was awarded to William R. Wallace. Edgar S. LaWall received honorable mention in connection therewith.

The Materia Medica Prize, \$25, offered by Prof. Clement B. Lowe, for the best examination in Materia Medica and in recog-

nition of *Materia Medica Specimens* with a meritorious thesis, was awarded to Anton Hogstad, Jr. The following graduates received honorable mention in connection therewith: Woods D. Balliet, Edgar S. LaWall, Elmer F. Merz, Nervin A. Myers, Stanley E. Sutton, Alvin C. Webb and Elwyn J. Wheeler.

The Microscopic Research Prize, a compound microscope, offered by Prof. Henry Kraemer, for the most meritorious thesis involving original microscopic work, was awarded to Anton Hogstad, Jr. The following graduates received honorable mention in connection therewith: Edmund E. Carr, Daniel J. Fry, Jr., William W. Heckenberger, Frank L. Kahler, Walter M. Kauffman, Norris D. Rowland, Edwin R. Spangler and Alvin C. Webb.

The Analytical Chemistry Prize, \$25, offered by Prof. Frank X. Moerk, for the best work in qualitative and quantitative analysis, was awarded to William R. Wallace. The following graduates received honorable mention in connection therewith: Stanley E. Sutton and Alvin C. Webb.

The Operative Pharmacy Prize, \$20 in gold, offered by Prof. Joseph P. Remington, for the best examination in Operative Pharmacy, was awarded to Stanley E. Sutton. The following graduates received honorable mention in connection therewith: Woods D. Balliet, Charles F. Kutteroff, Forrest S. Marshall, Edwin R. Spangler, Alvin C. Webb and Fred C. Wolverton.

The Maisch Botany Prize, \$20 in gold, offered by Mr. Joseph Jacobs, of Atlanta, Ga., was awarded to Alvin C. Webb, the presentation being made by Professor Kraemer. The following graduates received honorable mention in connection therewith: Edmund E. Carr, Daniel J. Fry, Jr., Walter M. Kauffman and Edwin R. Spangler.

The Mahlon N. Kline Theoretical Pharmacy Prize, a Troemner Agate Prescription Balance, for the best examination in Theory and Practice of Pharmacy, was awarded to Stanley E. Sutton, the presentation being made by Joseph W. England.

The Commercial Pharmacy Prize, \$20 in gold, offered by Prof. Joseph P. Remington to the graduate who passed the best examination in Commercial Training at the final examination for the degree, was awarded to John C. Gehrung, the presentation being made by Prof. E. Fullerton Cook. The following graduates received honorable mention in connection therewith: Joseph F. Botdorf, Louis Cohen, Meyer C. Epstein, Nervin A. Myers, Stanley E. Sutton, Alvin C. Webb and Elwyn J. Wheeler.

The Instructors' Prize, \$20, offered by the Instructors of the College, for the highest term average in the branches of Pharmacy, Chemistry and Materia Medica, was awarded to Stanley E. Sutton, the presentation being made by Prof. F. P. Stroup. The following graduates received honorable mention in connection therewith: Charles L. Gantert, Anthony LaCourse, Jr., Leo T. Trambley, Alvin C. Webb, Abram Weinstein and Elwyn J. Wheeler.

The Pharmacy Quiz Prize, one year's membership in the American Pharmaceutical Association, offered by Prof. Charles H. LaWall, for the best term work in Theory and Practice of Pharmacy, was awarded to Alvin C. Webb. The following graduates received honorable mention in connection therewith: Charles L. Gantert, Stanley E. Sutton, Leo T. Trambley, Abram Weinstein and Elwyn J. Wheeler.

The Special Lecture Report Prize, \$10 in gold, awarded for the best written reports of the series of special lectures held under the auspices of the College, session 1913-1914, was awarded to Charles F. Kutteroff, the presentation being made by Dr. A. W. Miller. The following graduates received honorable mention in connection therewith: Louis Cohen, Charles L. Gantert, Anton Hogstad, Jr., and Maurice Rosoff.

The Kappa Psi Fraternity Prize, a gold medal, offered by the Eta Chapter of the Kappa Psi Fraternity to the graduate making the highest general average during the senior year at the College, was awarded to Stanley E. Sutton, the presentation being made by George L. Holstein. The following graduates received honorable mention in connection therewith: Edgar S. LaWall, Alvin C. Webb and Elwyn J. Wheeler.

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## LEGEND AND SERIAL NUMBER ON INSECTICIDES AND FUNGICIDES ABOLISHED.

THE THREE SECRETARIES FIND THAT GUARANTY LEGEND ON SUBSTANCES USED TO DESTROY OR PREVENT INSECTS AND FUNGI IS DECEPTIVE AND MISLEADING. NO MORE SERIAL NUMBERS TO BE ISSUED OR GUARANTIES ACCEPTED.

Following their action prohibiting the use of a serial number and holding the guaranty legend on foods and drugs, under the Food and Drugs Act, to be deceptive, the Secretaries of the Treasury, Agriculture and Commerce, on June 30, signed an amend-

ment to the regulations under the Insecticide Act abolishing the use of serial numbers on insecticides and fungicides. The amended regulation also holds that the use of the legend "Guaranteed by (name of guarantor) under the Insecticide Act of 1910," on the labelling of insecticides and fungicides, or similar legends is misleading and deceptive in that the public is induced by such legend and serial number to believe that the articles to which they relate have been examined and approved by the Government.

The regulations, therefore, provide that the use of the guaranty legend or any similar legend on labels or packages of insecticides or fungicides, under which are included all substances for destroying or preventing insects or fungi affecting plants and animals, should be discontinued.

The new regulation is to become effective on and after May 1, 1916. In the case of products packed and labelled in accordance with the Insecticide Act and in conformance with the rules and regulations, prior to May 1, 1916, the amendment will become effective on and after November 1, 1916. Manufacturers, however, need not wait until May 1, 1916, to change their labels, but are free to make them conform to the new regulations at any time.

As in the case of the ruling on foods and drugs, the amended regulation as to insecticides and fungicides provide that where a wholesaler, manufacturer or jobber wishes to guarantee his goods so as to protect the dealer from prosecution, he may incorporate this guaranty in or attach it to the bill of sale, invoice, bill of lading, or other schedule. As the protection of the dealer and not a guaranty to the consumer was the original purpose of the legend, the new method fully protects the dealer without misleading the consumer.

In the meantime, the Department notifies the public that the presence of a serial number or guaranty legend on foods and drugs, or on insecticides and fungicides, in no way implies that the Government has tested or approved such articles, or guarantees them to be in compliance with the Federal law.

Office of Information

U. S. DEPT. OF AGRICULTURE,  
WASHINGTON, D. C.

# THE AMERICAN JOURNAL OF PHARMACY

AUGUST, 1914

A CRITICISM OF THE UNITED STATES PHARMACOPŒIA  
WITH RESPECT TO THE NAMING OF THE COM-  
POUND,  $C_{17}H_{21}NO_4 \cdot HBr + 3H_2O$ , AND WITH REGARD  
TO THE PRESCRIBED TESTS FOR ITS IDENTITY AND  
PURITY.

By A. G. DUMEZ,

Director of the School of Pharmacy, University of the Philippines.

ON THE ORIGIN AND USAGE OF THE TERMS HYOSCINE AND  
SCOPOLAMINE.

The term "hyoscin" was first used by Reichardt and Höhn<sup>1</sup> in 1871 to designate a basic substance,  $C_8H_{13}NO_2$ , obtained by the action of barium hydroxide upon hyoscyamine. In 1880, Ladenburg<sup>2</sup> isolated an alkaloid from the mother-liquor obtained in the preparation of the so-called amorphous hyoscyamine from the seeds of *Hyoscyamus niger*.<sup>4</sup> Ladenburg found the composition of this base to be repre-

<sup>1</sup> *Ann. d. Chem.* (1871), 157, p. 107.

<sup>2</sup> Later, the composition of this basic substance was found to be  $C_8H_{13}NO_2$  and became known under various names, in accordance with the fancies of the respective investigators—"pseudotropin" (Ladenburg), "oxytropin" (Ladenburg and Roth), "scopolin" (E. Schmidt), and "oscin" (Hesse).

The esters of the base  $C_8H_{13}NO_2$ , the acetyl-, benzoyl-, and cinnamyl-esters were manufactured by the firm of E. Merck previous to the year 1898, and were sold under the name of "Scopoleins," with the name of the acid radical as a prefix, *e.g.*, "acetyl-scopolein."—*Arch. d. Pharm.* (1898), 236, p. 33.

<sup>3</sup> *Ber. d. deutsch. chem. Ges.* (1880), 13, p. 1549.

<sup>4</sup> Bucheim was probably the first investigator to isolate the so-called "hyoscin." He obtained two basic substances from the seeds of *Hyoscyamus niger*, one of which he describes as being amorphous and oily, the other as being crystalline. To the former he gave the name "hyoscyamin" and to the latter the name "sikeranin." Cited by Ladenburg, *Ann. d. Chem.* (1881), 206, p. 283.

sented by the formula,  $C_{17}H_{23}NO_3$ , and thought it to be isomeric with hyoscyamine and atropine. He called it "hyoscin," as the compound obtained by Reichardt and Höhn was then thought to be identical with tropin, a decomposition product of hyoscyamine. In 1888, E. Schmidt and Henschke<sup>5</sup> obtained an alkaloid from the root of *Scopolia japonica*,<sup>6</sup> which, from the analysis and properties of its aurichloride, they concluded was identical with the "hyoscin" of Ladenburg. A year later, Bender<sup>7</sup> isolated hyoscyamine and what he thought was a new crystalline base from the root of *Scopolia atropoides*. A quantity of this crystalline base was sent to E. Schmidt for analysis. Bender describes the properties of this alkaloid as found by Schmidt under the name "scopolin." The analysis of the product led Schmidt to review carefully his former work on the base obtained from *Scopolia japonica*, with the result that he found the composition to be  $C_{17}H_{21}NO_4$  instead of  $C_{17}H_{23}NO_3$ , and that it was identical with the substance received from Bender. He gave it the name "scopolamin." Furthermore, Schmidt succeeded in obtaining this base,  $C_{17}H_{21}NO_4$ , from several other solanaceous plants and also from commercial hyoscyne hydrobromide, which was then being prepared by the firm of E. Merck. In fact, a base having the formula  $C_{17}H_{23}NO_3$  and corresponding to Ladenburg's "hyoscin" could never again be isolated from the mother-liquor resulting in the crystallization of hyoscyamine, its absence being conclusively proven by L. Merck<sup>8</sup> in 1897.

During the period of fifteen years following the work of Bender, the literature contains a considerable number of publications which tend to prove or disprove the identity of scopolamine and hyoscyne.

<sup>5</sup> *Arch. d. Pharm.* (1888), 226, p. 185.

<sup>6</sup> Langaard, in 1880, reported the isolation of two alkaloids from the root of *Scopolia japonica*, which he named "scopoleine" and "rotoine" respectively.—*Pharm. Journ.* (1881), 11, p. 10.

Three years later, Eykman, working with the same root, reported the presence of but one alkaloid, to which he also gave the name "scopolein." The base isolated according to the method of Eykman was being prepared and marketed by Merck of Darmstadt and Schuchardt of Gürlitz as early as 1888. Upon analysis, Schmidt found the product to be a mixture of "hyoscin" (Ladenburg), hyoscyamine, and atropine.—*Arch. d. Pharm.* (1888), 226, p. 187.

<sup>7</sup> *Chem. Zeitung* (1890), p. 805.

<sup>8</sup> *Arch. d. Pharm.* (1892), 220, p. 207.

<sup>9</sup> *Journ. Soc. Chem. Industr.* (1897), 16, p. 515.



some of which also tend to show the desirability of establishing the usage of the term scopolamine in preference to hyoscyne, or *vice versa*. The controversy was carried on principally by O. Hesse and E. Schmidt, with an occasional opinion from others.

In 1892, when Hesse<sup>10</sup> published his results on the identification of the Solanaceous alkaloids, he agreed with Schmidt that the composition of "hyoscin" (Ladenburg) should be represented by the formula  $C_{17}H_{21}NO_4$  and that it was identical with "scopolamin," but objected to the introduction of the latter term, as the hydrobromide had already been marketed for ten years under the name of "hyoscinhydrobromid." Later, however, Hesse concluded that the two were not identical, as "hyoscin" was known to be levorotatory, and he succeeded in isolating a quantity of an optically inactive base from commercial scopolamine hydrobromide. This led him to believe that "scopolamin" was a mixture of "hyoscin" and the new base to which he gave the name "atrosin."<sup>11</sup> As early as 1890, Schmidt<sup>12</sup> observed that the hydrobromide was levorotatory. He also discovered that solutions of the active scopolamine hydrobromide could be rendered optically inactive by the addition of small quantities of sodium or potassium hydroxide. This change he attributed to the conversion of the optically active base into an inactive isomer,<sup>13</sup> which he later isolated and called "inactive scopolamin." The identity of "atrosin" (Hesse) with the latter was conclusively proven by the work of Gadamer<sup>14</sup> and Kuntz-Krause<sup>15</sup> respectively.

The alkaloid represented by the formula,  $C_{17}H_{21}NO_4$ , was first placed upon the market in the form of the hydrobromide by Merck of Darmstadt. It was then being prepared from the base isolated from the seeds of *Hyoscyamus niger* and was sold under the name of "hyoscinhydrobromide." About 1894, shortly after the work of Bender and Schmidt, *scopolia* root became recognized as a source of supply. However, the hydrobromide, when prepared from the base obtained from the latter source, was marketed as "skopolamin-

<sup>10</sup> *Ann. d. Chem.* (1892), 271, p. 111.

<sup>11</sup> *Ber. d. deutsch. chem. Ges.* (1896), 29, p. 1781. The term "atrosin" has never received recognition by other investigators.

<sup>12</sup> *Arch d. Pharm.* (1892), 230, p. 207.

<sup>13</sup> *Ibid.* (1894), 232, p. 409.

<sup>14</sup> *Ibid.* (1898), 236, p. 382.

<sup>15</sup> *Journ. f. prakt. Chem.* (1910), 64, p. 569.

hydrobromid." Thus, E. Merck,<sup>16</sup> in 1896, remarked that the alkaloids, hyoscyne and scopolamine, were identical, but that the name hyoscyne was given to the base when isolated from *Hyoscyamus niger*, while the term scopolamine was applied to that isolated from *scopolia* root.

In 1897, L. Merck<sup>17</sup> called attention to some observations indicating that the hydrobromide prepared from the alkaloid obtained from *Hyoscyamus niger* was fairly constant, showing a specific rotatory power of  $-24^{\circ}$  to  $-25^{\circ}$ ; while that prepared in a like manner from the alkaloid when obtained from *scopolia* root varied and showed a much lower specific rotatory power,  $-13.47^{\circ}$ .<sup>18</sup> From the foregoing observations one would naturally infer that the designation hyoscyne hydrobromide would insure a product strongly levorotatory and containing little of the optically inactive isomer, while the term scopolamine hydrobromide would indicate a salt having a low specific rotatory power. Such, however, is not the case, exactly the reverse being true at the present time. The observations of Schmidt,<sup>19</sup> Hesse,<sup>20</sup> Luboldt,<sup>21</sup> and others show that the commercial salt, the hydrobromide, regardless of its natural source, often varied in its rotatory power. Schmidt attributed this variation, in the case of the salt prepared from *Hyoscyamus niger*, to the use of strong alkalies, such as the hydroxides of sodium and potassium, or even their normal carbonates on long standing, in the isolation of the free base. Furthermore, it was found that the name given to the commercial product was no indication of this variation, the salt designated hyoscyne hydrobromide varying as well as that bearing the name scopolamine hydrobromide. However, upon the introduction into the German Pharmacopœia<sup>22</sup> of the term "Skopolamin-

<sup>16</sup> Merck's Bericht (1894), p. 94.

<sup>17</sup> Journ. Soc. Chem. Industr. (1897), 16, p. 515.

<sup>18</sup> Schmidt noted a specific rotatory power of  $-25^{\circ} 43'$  for scopolamine hydrobromide prepared from the base obtained from the root of *Scopolia atropoides*. He is of the opinion that the low rotatory power observed by Merck was due to the presence of i-scopolamine which may preëxist in the plant at certain seasons of the year or which may be formed in the process of curing.—Arch. d. Pharm. (1898), 236, p. 59.

<sup>19</sup> Apoth. Ztg. (1896), 11, p. 260.

<sup>20</sup> Ibid. (1895), 10, p. 187.

<sup>21</sup> Arch. d. Pharm. (1898), 236, pp. 11-47.

<sup>22</sup> Deutsches Arzneibuch, 5th Edit., Berlin (1910), p. 451.

hydrobromid" with the specific rotatory power as a test for its identity and purity, German manufacturers began producing the lævo-salt to the exclusion of that having little or no rotatory power. Hence the name scopolamine hydrobromide, in Germany at least, now signifies the lævo-compound.

That the present tendency in England is to apply the name scopolamine hydrobromide in a manner similar to that of the German Pharmacopœia, while hyoscine hydrobromide is being used to designate the salt having the weaker rotatory power, is evidenced in the following:

(a) Spencer Sheill<sup>23</sup> states that scopolamine is used by some to represent the lævo-compound, while hyoscine is applied by others to the mixture of the lævo- and inactive varieties having the weaker rotatory power.

(b) A statement similar to the latter is also given in the Extra Pharmacopœia of Martindale and Westcott.<sup>24</sup>

(c) Finnemore and Braithwaite<sup>25</sup> report that English physicians use the term scopolamine hydrobromide when prescribing rather than hyoscine hydrobromide in order to be sure of securing the German preparation, which is lævorotatory.

From the survey of the literature, it appears that the designation hyoscine hydrobromide is still given preference in the United States, although practically all of the salt is imported from Germany and is now being received largely as the lævo-variety.

A more concrete idea of the variations in the naming of the alkaloid and its salt, the hydrobromide, may be obtained from the following tabulations:

TABLE NO. 1.

NAMES APPLIED TO THE FREE BASE OR RELATED COMPOUNDS.

Atroscin....	{ Hesse, 1896 = $C_{17}H_{21}NO_4$ , isolated from commercial scopolamine hydrobromide, optically inactive and identical with i-scopolamine.
	{ Reichardt and Höhn, 1871 = $C_8H_{15}NO$ , a decomposition product of hyoscyamine.
Hyoscine....	{ Ladenburg, 1880 = $C_{17}H_{23}NO_3$ , isolated from <i>Hyoscyamus niger</i> .
	{ Schmidt and Henschke, 1888 = a base isolated from <i>Scopolia japonica</i> .
	{ Hesse, 1892 = $C_{17}H_{21}NO_4$ , isolated from <i>Hyoscyamus niger</i> .
	{ E. Merck, 1894 = $C_{17}H_{21}NO_4$ , isolated from <i>Hyoscyamus niger</i> .

<sup>23</sup> *Lancet* (1910), 11, p. 29.<sup>24</sup> Martindale and Westcott, Extra Pharmacopœia, London (1912), p. 444.<sup>25</sup> Year-Book of Pharm. and Trans. (1912), p. 498.

	Schmidt, 1890 = $C_{17}H_{21}NO_4$ , isolated from <i>Scopolia japonica</i> .
	Schütte, 1891 = $C_{17}H_{21}NO_4$ , isolated from <i>Datura stramonium</i> .
Scopolamin.	Schmidt, 1892 = $C_{17}H_{21}NO_4$ , isolated from <i>Datura stramonium</i> , <i>Duboisia myoporoides</i> , and <i>Atropa belladonna</i> .
	E. Merck, 1894 = $C_{17}H_{21}NO_4$ , isolated from <i>Scopolia</i> root.
	Thoms and Wentzel, 1898 = $C_{17}H_{21}NO_4$ , isolated from <i>Mandragora</i> root.
Inactive Scopolamin.	Schmidt, 1896 = $C_{17}H_{21}NO_4$ , the optically inactive isomer.
Scopoleine.	Langaard, 1881 = a mixture of alkaloids from <i>Scopolia japonica</i> , principally $C_{17}H_{21}NO_4$ .
Scopoleins.	Firm of Merck, 1898 = esters of the base, $C_8H_{13}NO_2$ .
Scopolin.	Bender, 1890 = $C_{17}H_{21}NO_4$ , isolated from <i>Scopolia japonica</i> .

TABLE NO. 2.

## OFFICIAL NAMES AND SYNONYMS OF THE HYDROBROMIDE.

Hyoscine hydrobromicum.....	
Hyoscine hydrobromide.....	
Hydrobromate of hyoscine.....	British Pharmacopœia, 1898.
Scopolamine hydrobromide.....	
Hyoscine hydrobromidum.....	
Hyoscine hydrobromide.....	
Hyoscine hydrobromas, 1890.....	United States Pharmacopœia, 1905.
Scopolamine hydrobromidum.....	
Scopolamine hydrobromide.....	
Neither the free base nor its salt, the hydrobromide, is official.....	French Pharmacopœia, 1908.
Bromidato di Scopolamina.....	Italian Pharmacopœia, 1909.
Scopolaminum hydrobromicum.....	German Pharmacopœia, 1910.
Skopolaminhydrobromid.....	

## ON THE PHYSIOLOGICAL ACTION OF SCOPOLAMINE.

Scopolamine is an ester of tropic acid and the base, scopolin.<sup>26</sup> and, like the closely related hyoscyamine, may exist in three stereoisomeric forms. Two of these, the lævo- and racenic forms, are known. These isomers, like those of nicotine<sup>27</sup> and hyoscyamine,<sup>28</sup> differ in their physiological action as well as in their chemical and physical properties.

The early investigators who attempted to discover a difference in the physiological action of the two isomers did not work with the material prepared in their own laboratories, and very probably used the salts in an impure state; i.e., as mixtures of the two isomers or with small amounts of other impurities<sup>29</sup> present. Add to this

<sup>26</sup> Gadamer, *Arch. d. Pharm.* (1901), 239, p. 321.

<sup>27</sup> *Ber. d. deutsch. chem. Ges.* (1904), 37, p. 1234.

<sup>28</sup> Cushny, *Journ. of Physiol.* (1904), 30, p. 176.

<sup>29</sup> Schmidt, Scopolamine hydrobromide with a low specific rotatory power contains a small amount of an impurity not easily detected.—*Arch. d. Pharm.* (1905), 243, p. 4.

the lack of chemical knowledge concerning the substance with which they were working and we can readily understand why they obtained varying and sometimes contradictory results.

Königshoefer<sup>30</sup> reported that the effect of atropine (i-scopolamine) upon the accommodation takes place with greater rapidity and is of longer duration than in the case of scopolamine (l-scopolamine). Under pathological conditions (iritis) he also found its action to be the more energetic.

Meyer confirmed<sup>31</sup> the latter finding, but stated that he could not agree with Königshoefer with respect to the action on the accommodation.

Uhthoff and Axenfeld<sup>32</sup> could find no difference in the physiological action of scopolamine hydrobromide having a specific rotatory power of  $-25.43^\circ$  and that having specific rotatory power of  $-6.62^\circ$ .

In more recent years the work has been taken up with a greater knowledge of the chemistry of the isomers and under more advantageous conditions, with the result that real differences in their physiological activity have been found and clearly described.

Cushny and Peebles<sup>33</sup> found:

(a) That the action of l-scopolamine on the terminations of the secretory nerves in the salivary glands and on the terminations of the inhibitory fibres of the heart was double that of i-scopolamine in effect; from which they inferred that a similar ratio might hold in other analogous terminations.

(b) That l- and i-scopolamine produce the same effect in a like degree upon the central nervous system in man and mammals and on the terminations of the motor nerves in the frog.

E. Hug,<sup>34</sup> from a series of experiments on dogs and cats, concluded:

(a) That the action of l-scopolamine on the vagus is three to four times as great in strength as that of i-scopolamine.

(b) That l-scopolamine acts twice as energetically as i-scopolamine upon the oculomotorius.

Evidence to the effect that a difference in the physiological action

<sup>30</sup> Cited by Hesse, *Ber. d. deutsch. chem. Ges.* (1896), 27, p. 1781.

<sup>31</sup> Cited by E. Schmidt, *Arch. d. Phar.* (1897), 236, p. 71.

<sup>32</sup> Cited by L. Merck, *Pharm. Journ.* (1897), 71, p. 41.

<sup>33</sup> *Journ. of Physiol.* (1905), 32, pp. 501-510.

<sup>34</sup> *Arch. f. exp. Path. u. Pharmac.* (1912), 69, p. 56.

of the commercial preparations has been observed by medical practitioners is amply supplied in the literature. In fact, the references are too numerous to be included in this paper. However, the statement of Finnemore and Braithwaite<sup>35</sup> in connection with the use of hyoscine and scopolamine hydrobromides by English physicians is quoted because of the direct application:

"Anæsthetists have expressed a preference for the German preparations sold under the name of 'Scopolamine hydrobromide' owing to the variable results obtained following the administration of the product known as 'Hyoscine hydrobromide.'"

### ON THE TESTS FOR IDENTITY AND PURITY.

The chemical and physical properties of scopolamine and its salts have been quite thoroughly worked up by E. Schmidt, O. Hesse, Gadamer, and others. There is, however, some uncertainty concerning the melting-points of the chloraurates of both the l- and i-scopolamine, the greater number of the investigators confirming the results obtained by Schmidt. The following tables show the important physical constants of the hydrobromides as obtained by various investigators and as given in the United States, British, and German Pharmacopœias:

TABLE NO. 3.

Name of investigator.	Stereo-isomer.	M. P. of the anhydrous salt.	M. P. of the chloraurate.	M. P. of the hydrobrom-chloraurate.	M. P. of the picrate.	Specific rotatory power in aqueous solution.
E. Schmidt <sup>36</sup> .....	Lævo-	193-194°	212-214°	.....	187-188°	-25° 43'
E. Schmidt.....	Inactive	180°	208-210°	.....	.....	0°
Gadamer <sup>37</sup> .....	Inactive	.....	208°	.....	.....	0°
Kircher <sup>38</sup> .....	Lævo-	.....	208-209°	.....	.....	-25° 52'
Thoms and Wentzel <sup>39</sup> .....	.....	.....	205°	.....	.....	-25.7° to
O. Hesse <sup>40</sup> .....	Lævo-	192-197°	198°	.....	.....	-25.0°
O. Hesse.....	Inactive	181°	201-202°	.....	.....	0°
Jowett <sup>41</sup> .....	Lævo-	.....	.....	About 215	.....	.....

<sup>35</sup> Year-Book of Pharm. and Trans. (1912), p. 498.

<sup>36</sup> *Arch. d. Pharm.* (1898), 236, p. 59.

<sup>37</sup> *Ann. d. Chem.* (1900), 310, p. 352.

<sup>38</sup> *Arch. d. Phar.* (1905), 243, p. 321.

<sup>39</sup> *Ber. d. deutsch. chem. Ges.* (1898), 31, p. 2037.

<sup>40</sup> *Journ. f. prakt. Chem.* (1901), 64, 2, p. 364.

<sup>41</sup> *Journ. Chem. Soc.* (1897), 71, p. 678.

In explanation of the table it should be stated that Schmidt and Gadamer determined the melting-points of the various salts, using a capillary tube and sulphuric acid bath; Hesse used a "Roth's" apparatus. Schmidt found the melting-point of the chloraurate of the l- salt to be  $208^{\circ}$  to  $209^{\circ}$  when determined with the "Roth's" apparatus.<sup>42</sup>

TABLE NO. 4.

Pharmacopœia.	Per cent. of H <sub>2</sub> O lost in drying at $100^{\circ}$ C. or over H <sub>2</sub> SO <sub>4</sub>	M. P. of the anhydrous salt.	M. P. of the chloraurate.	Specific rotatory power of a 5 per cent. aqueous solution at $15^{\circ}$ C.
United States <sup>43</sup> .	.....	$179.7^{\circ}$	$197^{\circ}$	.....
British <sup>44</sup> .	More than 12 per cent.	$193-194^{\circ}$	$198^{\circ}$	.....
German <sup>45</sup> .	12.3 per cent.	About $190^{\circ}$	....	$-24^{\circ} 45'$

A comparison of the constants as given in Tables No. 3 and No. 4 shows the melting-point ( $179.7^{\circ}$  C.) of the anhydrous hydrobromide as specified in the United States Pharmacopœia to agree very closely with that ( $180^{\circ}$  C.) found by Schmidt or Hesse ( $181^{\circ}$  C.) for i-scopolamine hydrobromide; while the melting-point ( $197^{\circ}$  C.) of the chloraurate as given in the pharmacopœia corresponds very well with that ( $198^{\circ}$  C.) found by Hesse for the chloraurate of l-scopolamine. According to two observers, the melting-point of the hydrobromide alone is no indication as to the respective quantities of the l- and i-isomers present in the commercial salt; *e.g.*, Schmidt<sup>46</sup> found a melting-point of  $180^{\circ}-181^{\circ}$  C. for the commercial hydrobromide,  $[\alpha]_D = -13^{\circ} 30'$ ; Hesse<sup>47</sup> obtained a melting-point of  $178^{\circ}$  C. for a sample of the hydrobromide,  $[\alpha]_D = -21.3^{\circ}$ . If we take into consideration the fact that the hydrobromides of both the lævo- and the inactive forms crystallize with  $3\text{H}_2\text{O}$ , and that the melting-points of the chloraurates have not yet been definitely established, it becomes evident that the pharmacopœial tests for the identity of this compound are worthless.

That physical constant which has been found to give the most accurate indication as to the purity of l-scopolamine or its salts,

<sup>42</sup> Arch. d. Phar. (1894), 232, p. 417.

<sup>43</sup> U. S. P., 8th Rev. (1905), p. 391.

<sup>44</sup> British P. (1898), p. 153.

<sup>45</sup> Deutsches Arzneibuch, 5th Edit., Berlin (1910), p. 451.

<sup>46</sup> Arch. d. Pharm. (1898), 236, p. 62.

<sup>47</sup> Journ. f. prakt. Chem. (1901), 64, 2, p. 385.

both with respect to the presence of the inactive variety and to foreign substances, is the specific rotatory power. This has been found to be between  $-24^{\circ}$  and  $-25^{\circ}$  for the fairly pure anhydrous hydrobromide in a 5 per cent. aqueous solution at  $15^{\circ}$  C. A specific rotatory power of  $-32.3^{\circ}$  to  $-32.9^{\circ}$  has been found by Hesse<sup>48</sup> for the salt in a high state of purity. Determinations of this constant have revealed the following variations in the commercial product:

1894—E. Schmidt<sup>49</sup>: Scopolamine hydrobromide from Gehe and Company, Dresden.  $[\alpha]_D = -14.58^{\circ}$ .

1895—E. Schmidt<sup>50</sup>: Scopolamine hydrobromide from E. Merck, Darmstadt.  $[\alpha]_D = -17^{\circ} 9'$ .

1895—Gadamer<sup>51</sup>: Scopolamine hydrobromide from Gehe and Company, Dresden. Anhydrous salt in aqueous solution,  $p = 6.3043$ ,  $t = 19.8^{\circ}$  C.,  $[\alpha]_D = -6.62^{\circ}$ .

1896—O. Hesse<sup>52</sup>: Five commercial samples of scopolamine hydrobromide showed a specific rotatory power as follows:  $-22.1^{\circ}$ ,  $-12.7^{\circ}$ ,  $-12.1^{\circ}$ ,  $-11.3^{\circ}$ ,  $-10.0^{\circ}$ .

1897—L. Merck<sup>53</sup>: Scopolamine hydrobromide from *Scopolia* root,  $[\alpha]_D = -13.47^{\circ}$ . Scopolamine hydrobromide from the seed of *Hyoscyamus niger*,  $[\alpha]_D = -24^{\circ}$  to  $-25^{\circ}$ .

1898—Luboldt<sup>54</sup>: Scopolamine hydrobromide from Gehe and Company, Dresden. 1.5304 Gm. of anhydrous salt in aqueous solution,  $d = 1.0096$ ,  $t = 15^{\circ}$ ,  $[\alpha]_D = 14^{\circ} 58'$ .

1899—O. Hesse<sup>55</sup>: Scopolamine hydrobromide, commercial. Anhydrous salt in aqueous solution,  $p = 4$ ,  $t = 15^{\circ}$ ,  $[\alpha]_D = -7.5^{\circ}$ .

1901—Gadamer<sup>56</sup>: Scopolamine hydromide from E. Merck, Darmstadt.  $[\alpha]_D = -24.69^{\circ}$ .

1912—E. Hug<sup>57</sup>: Scopolamine hydrobromide from Hoffmann-La Roche Company, Grenzach. Anhydrous salt in aqueous solution,  $p = 4.5$ ,  $[\alpha]_D = -26.0^{\circ}$ .

1912—Finnemore and Braithwaite<sup>58</sup>: Four samples of commercial hyoscyne hydrobromide showed a specific rotatory power as follows:  $-23^{\circ} 7'$ ,  $-21^{\circ} 59'$ ,  $-21^{\circ} 25'$ ,  $-6^{\circ} 30'$ ; one sample was found to be inactive.

<sup>48</sup> Journ. f. prakt. Chem. (1901), 64, 2, p. 385.

<sup>49</sup> Apoth. Ztg. (1896), 11, p. 260.

<sup>50</sup> Ibid.

<sup>51</sup> Cited by Schmidt, Arch. d. Pharm. (1898), 236, p. 47.

<sup>52</sup> Ber. d. deutsch. chem. Ges. (1896), 29, p. 1780.

<sup>53</sup> Journ. Soc. Chem. Industr. (1897), 16, p. 575.

<sup>54</sup> Arch. d. Phar. (1898), 236, p. 14.

<sup>55</sup> Ann. d. Chem. (1899), 309, p. 90.

<sup>56</sup> Arch. d. Phar. (1901), 239, p. 324.

<sup>57</sup> Arch. f. exp. Path. u. Pharmak. (1912), 69, p. 48.

<sup>58</sup> Phar. Journ. and Trans. (1912), p. 498.



## CONCLUSIONS AND SUGGESTIONS.

1. Practically all of the scopolamine hydrobromide or the so-called hyoscyne hydrobromide consumed in the United States is at present supplied by Germany, where the lævo-compound only is recognized as official under the title "Skopolaminhydrobromid." In view of this fact, and as present usage, not only in Germany but in other continental countries and in England, indicates a preference for the latter term, there can be no important reason for the same compound appearing under two different titles in the United States Pharmacopœia. It is therefore suggested that the term "Scopolamine hydrobromide" be made the official English title in the next revised edition of the pharmacopœia, with "Hyoscyne hydrobromide" as a possible synonym.

2. As there is still some doubt concerning the exact melting-point of the chloraurate of either the l- or i-scopolamine, this constant should not be prescribed as a test by the next pharmacopœia.

3. It is now known that scopolamine or the so-called hyoscyne may exist in either the lævo- or inactive forms, and that the commercial hydrobromide is usually the lævo-salt, but not infrequently a mixture of the two isomeric forms. It is also known that the isomers produce different physiological effects, the lævo- variety preferred by medical practitioners because of its particular physiological action and on account of its constant state of purity. It is therefore suggested that the revised edition of the United States Pharmacopœia recognize only the l-scopolamine hydrobromide as official, and that a definite specific rotatory power be prescribed for it.

## CONSTITUENTS OF ANDROGRAPHIS PANICULATA.

By KSHITIBHUSHAN BHADURI, M.Sc.

*Andrographis paniculata*, Nees (Fam. *Acanthaceæ*), is a common bitter plant growing throughout the plains of India. The plant is an annual one, two to three feet long; stem quadrangular, pointed, smooth; leaves opposite, on short petioles, lanceolate, entire upper surface dark green and shining, under surface paler and finely granular; they vary much in size, but the larger are usually three inches in length and one inch in breadth; calyx deeply five-cleft, corolla bilabiate, tips linear, reflected, upper one three-toothed, lower

one two-toothed; flowers remote, alternate, long petioles, downy, rose colored or white streaked with purple; capsules erect, somewhat cylindrical; seeds, three to four in each; roots fusiform, simple woody with numerous fine radicles.

The plant is well known in Bengal under the name of Kalmegh, and is the principal constituent of a domestic medicine named Alui which is given to children for the relief of griping, irregularity of bowels, and loss of appetite. It is also called Kiryat, and is used as a substitute for chirata. It is called in Sanskrit "Mahatikta," or king of bitters.

According to Dr. W. A. Boorsma (Mededeelingen uit S Lands plantentium, 1896, xviii, 63), if the powdered plant be mixed with lime and submitted to steam distillation, the distillate gives all the tests of a volatile alkaloid which he could not isolate. He, however, isolated an amorphous bitter substance ( $C_{15}H_{27}O_4$ ).

He says that the substance begins to decompose before melting, so that he could not determine its melting-point accurately. The amorphous substance obtained by the present author has some properties common with the above substance, but the melting-point has been accurately determined; while the above author says, that the amorphous and crystalline (also obtained by him) substances have the same properties, the two substances described herein have very different properties.

Dr. K. Gorter, by extracting the leaves of *Andrographis paniculata* with alcohol, obtained a lactone ( $C_{22}H_{30}O_5$ ) named andrographolite. It is converted into salts of andrographic acid by boiling with caustic alkalies (*Apoth. Zeits.*, 1911, 26, 954).

#### EXPERIMENTAL.

For examination 68 Gm. of the powdered leaves and stems were taken and exhausted in a Soxhlet apparatus successively by petroleum ether, ether, chloroform, and alcohol; after evaporation of the solvents the extracts weighed:

Petroleum ether .....	0.437	Gm., or 0.643 per cent.
Ether .....	0.5864	Gm., or 0.861 per cent.
Chloroform .....	2.2501	Gm., or 3.309 per cent.
Alcohol .....	1.5045	Gm., or 2.214 per cent.
Total .....	7.027	per cent.

55 Gm. of substance on burning gave 9.7802 Gm. or 17.782 per cent. of ash.

The plant is very rich in chlorophyll, one portion of which is soluble in chloroform and the other not, though both are soluble in alcohol.

#### EXAMINATION OF THE PETROLEUM ETHER EXTRACT.

This was a viscid, brownish-yellow colored liquid from which, on keeping a small quantity of an inactive, needle-shaped crystalline substance separated out, having  $117^{\circ}$  C. as its melting-point, the quantity obtained was so small that no further examination was possible. The viscid mass also contained a little essential oil, which was separated by extraction with alkalies; the rest of it was "kalmegh resin," a portion of which was extracted by first making it alkaline with caustic potash and shaking up with ether. It can be further extracted with ether after acidification with an acid.

#### CHLOROFORM EXTRACT.

This contained besides chlorophyll an amorphous white substance and very little of a bitter substance, the former of which separated out on concentrating the chloroform extract. Its melting-point is  $221^{\circ}$  C. It is tasteless and insoluble in water and alcohol. It is unacted upon by acids and alkalies.

#### EXTRACTION OF THE BITTER PRINCIPLES.

For this extraction the powdered leaves and stems were exhausted in a percolator with alcohol, almost the whole of which was distilled off. The thick, viscid mass left in the flask was then submitted to steam distillation. Two or three drops of an essential oil first came over; this had an intensely characteristic odor suggesting that of the dried plant. The distillation continued till the whole of the alcohol was distilled off. The residue remaining in the flask separated into two layers, one aqueous and the other solid; the former when allowed to cool deposited some yellow colored crystals (bitter *a*); the latter was boiled with water and filtered hot; from the filtrate a white amorphous precipitate was deposited having an extremely bitter taste (bitter *b*).

## EXAMINATION OF THE BITTER PRINCIPLE (A).

This was purified by dissolution in alcohol and fractional precipitation; the process was repeated three times. It had a pale yellow color. When a little of the substance was heated in a test-tube it diffused a very fragrant odor. It had melting-point of  $206^{\circ}$  C.

Strong sulphuric acid produced a yellowish-brown color. With potassium dichromate and sulphuric acid the substance at first gave a deep brown (almost black) color, attended with brisk effervescence. After a time the effervescence ceased and the color passed to grass-green.

Strong sulphuric acid containing a trace of nitric acid produced a reddish-brown color.

Strong sulphuric acid containing ammonium vanadate produced brownish-red color, changing to green.

In strong nitric acid the substance dissolved readily, the solution acquiring a yellow color.

The substance is very soluble in ethyl and methyl alcohol, though not to the above extent in amyl alcohol. It is very slightly soluble in chloroform and ether. Benzene and petroleum ether do not dissolve it even on boiling.

It is neither an alkaloid nor a glucoside, as it neither contains nitrogen nor produces a reducing sugar after hydrolysis. It can be acetylated,—i.e., it contains hydroxyl groups; the acetyl derivative is white and insoluble in water. Its melting-point is  $95^{\circ}$  C.

When the substance was added to a solution of bromine in chloroform a dark-colored oil separated out; on washing the latter with a dilute solution of potassium carbonate a white solid substance was left behind. This was the bromo derivative of the bitter; the direct absorption of bromine proves the presence of at least one double bond. The melting-point of the bromo derivatives would not be determined, as it began to decompose at  $120^{\circ}$  C. before melting; at  $160^{\circ}$  C. it was a liquid, but began to give off a quantity of gas.

0.0498 Gm. of the bromo derivative gave 0.0160 Gm. of AgBr or 13.7 per cent. of bromine. Since there must be at least two atoms of bromine in the molecule, the molecular weight is 1175 or some multiple of it.

0.1008 Gm. of the bitter analysis gave 0.2521 Gm. of  $\text{CO}_2$  and 0.0763 Gm. of  $\text{H}_2\text{O}$ .

Hence C 68.2, H 8.4.

The simplest formula is  $C_{19}H_{28}O_5$ .

The molecular weight of the bitter principle as determined from the bromo-compounds is 1015, which is exactly six times that of the empirical formula.

The acetyl derivative gave the following analytical data:

It contains 1.74 per cent. of water.

0.0697 Gm. of it gave 0.1863 Gm. of  $CO_2$  and 0.05056 Gm. of  $H_2O$ .

Hence C 76.2 H 8.06.

#### EXAMINATION OF THE BITTER PRINCIPLE (B).

It was a white amorphous substance having an extremely bitter taste. It is odorless, and its melting-point is  $185^\circ C$ . It is practically insoluble in cold water. When a little of the substance was boiled for a long time with water the latter acquired a slightly acid reaction. It is soluble in alcohol and chloroform. In the Pharmacographia of Fluckiger and Hanbury it is said that an infusion gives a voluminous precipitate with tannic acid, but this property was altogether found to be absent. Most probably in the former case the precipitate was due to the presence of some albuminous matter. Sulphuric acid produces an orangish-yellow color; when potassium dichromate is added to the above the color changes as one to yellow-green, which through greenish-brown finally passes to deep grass-green. If the substance be mixed with potassium dichromate before the addition of sulphuric acid, and the acid then added, the color first produced is brown, but the final color in this case also is deep grass-green.

Strong sulphuric acid containing a trace of nitric acid gives a brown color.

Strong sulphuric acid containing a trace of ammonium vanadate produces a brown color, changing to violet.

Strong nitric acid does not produce any change.

0.409 Gm. gave 0.0448 Gm. of  $H_2O$  and 0.0930 Gm. of  $CO_2$ .  
 C 62.01, H 14.88 and O 23.01.

The formula  $C_{19}H_{28}O_5$  is given to it, for which the theoretical values are—

C 62.24, H 14.7 O 23.01.

The name Kalmeghin is proposed for it.

A white substance separated out when bitter (b) was treated with an acid.

This was washed with water and dried. It had an acid reaction and was soluble in alkalies, neutralizing it. As it was derived from Kalmeghin the name Kalmeghic acid was given to it.

0.043 Gm. gave 0.0699 Gm. of  $H_2O$  and 0.2053 Gm. of  $CO_2$ .

Hence C 75.23 H 10.4.

The formula is  $C_{14}H_{23}O_2$ .

This acid, as well as the bitter principle (b), gave fluorescein test, showing the presence of a benzene nucleus with two adjacent side chains.

CHEMICAL LABORATORY, PRESIDENCY COLLEGE, BENGAL.

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## ON THE DETERMINATION OF ACETANILID.

By DR. A. MIRKIN, Cincinnati, Ohio.

The determination of acetanilid in tablets is still effected by an extraction with chloroform, the chloroform being collected in a tared flask, evaporated, and the residue dried at a low temperature and weighed. This method frequently gives low results on account of the volatility of acetanilid, and very often it is not applicable at all on account of the presence of other ingredients in the tablets which are also soluble in chloroform.

The volumetric method adopted by the Association of Official Agricultural Chemists, in which a solution of potassium bromide-bromate is used, does not always give accurate results, and it seemed desirable to find another method which might prove successful when other methods failed.

Bay and Vignon (*Comptes Rend.*, 135, 507; *Centralblatt*, 1902, ii, 1094) determine nitrous acid by titrating with a standard solution of aniline. The nitrous acid is used up in diazotizing the aniline. As soon as the nitrous acid is gone a piece of potassium iodide-starch paper, with which the solution is tested from time to time, does not turn blue any more. This reaction is reversible, and one can titrate aniline with a standardized solution of sodium nitrite. By converting acetanilid into aniline and titrating with a standard sodium nitrite solution, we have a quick method of determination. In order to obtain correct results all the conditions mentioned below must be strictly adhered to.

One gramme of acetanilid is boiled for four hours with a mixture of one part sulphuric acid (sp. gr. 1.84) and five parts water. The solution is then cooled and carefully neutralized with sodium bicarbonate. HCl is then added (6 mol. to 1 mol. anilin) and the flask is cooled to  $-10^{\circ}$  by throwing in pieces of ice and using a freezing mixture. The sodium nitrite is then slowly added from a burette with thorough shaking of the flask after each addition. From time to time the solution is tested with potassium iodide-starch paper. It frequently happens that the potassium iodide-starch paper turns blue even when there is unchanged aniline. This is due to the low temperature, which causes the diazotizing to take place slowly. One must therefore not be too hasty in his conclusions, especially at the end, but wait several minutes after the addition of sodium nitrite before applying the KI-starch paper test.

As mentioned above, Bay and Vignon, the originators of this method, should be given full credit. I have only adapted their method of determining aniline to the determination of acetanilid.

## PREPARATION AND ANALYSES OF VLEMINCKX'S SOLUTION.<sup>1</sup>

By JOSEPH L. MAYER.

A short time ago two samples of Vleminckx's Solution were submitted to me with a request that in view of the fact that the color of one sample was markedly different from the other, analyses be made to ascertain if they were properly prepared.

Since the National Formulary only contains a formula for the preparation, and various pharmaceutical authorities consulted made no reference to a standard, it was necessary to make samples in an effort to determine how the solution should be prepared and what the strength of the finished product should be. The following work was therefore undertaken.

Referring to page 81, 3rd edition of the National Formulary, we found that "Liquor Calcis Sulphuratæ"—"Vleminckx's Solution"—was directed to be prepared as follows:

Lime, freshly slaked ..... 165 grammes.  
Sublimed sulphur ..... 250 grammes.  
Water, a sufficient quantity to make 1000 grammes.

<sup>1</sup> Read before the Kings County Pharmaceutical Society, May 12, 1914.

Mix the slaked lime with the sulphur, and add the mixture gradually to 1750 c.c. of boiling water. Then boil the whole, under constant stirring, until it is reduced to 1000 grammes, strain, and having allowed the solution to become clear by standing in a well-stoppered bottle, decant the clear brown liquid, and keep it in completely filled and well-stoppered bottles.

We accordingly made up one-tenth of this formula by taring a 600 c.c. porcelain evaporating dish, adding 175 c.c. of water heating to boiling and then slowly adding the mixture of freshly slaked lime and sulphur, constantly stirring while heating until the weight was reduced to 100 grammes. The material was then decanted into a 4 oz. cork stoppered bottle, allowed to stand until the next day, filtered and assayed for total sulphur by the following method:

"Measure 10 c.c. of the clear sample in a 100 c.c. measuring flask and fill to the mark. Analyze 10 c.c. aliquots of this solution. Treat with 3 c.c. of saturated solution potassium hydroxide or sodium hydroxide solution, following by 50 c.c. hydrogen peroxide free from sulphates. Heat on the steam bath for one-half hour exactly and then acidify with hydrochloric acid, precipitate with barium chloride in the usual way in boiling solution, and finally weigh as barium sulphate." Of course multiplying the weight of barium sulphate by the proper factor gives the quantity of sulphur and this multiplied by 100 gives the percentage.

We ran blanks on the reagents and determined the quantity of sulphate present, which was then deducted from that found in the actual analysis.

This is Avery's method, and is suggested by the Association of Official Agricultural Chemists for the analysis of lime-sulphur dips and lime-sulphur-salt mixture (U. S. Dept. Agr. Bureau of Chemistry, Bul. 107, rev. page 34); it is an extremely accurate and simple one which in our hands yielded remarkably close duplicates.

We also analyzed the sample for total sulphur in solution, monosulphur equivalent, thiosulphate sulphur, sulphate and sulphite sulphur, total sulphide sulphur and total lime (CaO) in solution following the method in U. S. Dept. Agr. Bureau of Chemistry, Bul. 162, page 29, but seeing no advantage over the Avery method, employed that in all our analyses and simply determined the total sulphur, of which the above sample showed the presence of 10.838 grammes in 100 c.c. of solution.



Another 100 gramme lot made up in the same manner contained 14.581 grammes of total sulphur in 100 c.c. of solution.

This great variation in results indicated difficulty in properly preparing the solution. We, therefore, referred to the direction in the N. F. and found it directed to add the lime and sulphur mixture "gradually to 1750 c.c. of boiling water. Then boil the whole under constant stirring until it is reduced to 1000 grammes;" this procedure differs from mine in that it directs the water to be heated to boiling, the mixture of lime and sulphur added and the whole boiled under constant stirring until the weight is reduced to 1000 grammes.

Another 100 gramme lot was then made by strictly adhering to these directions and when assayed showed the presence of 4.448 grammes of total sulphur in 100 c.c. solution.

My original reading of the process was as above noted to heat the water to boiling and then while the water was still on the fire to gradually add the lime and sulphur under constant stirring and boiling until the proper weight was produced, whereas the last product was made by strictly following the N. F. by heating the water to boiling, taking it off the fire, stirring all the lime and sulphur in, putting it back on fire, stirring and heating until the proper weight was attained.

The above figures clearly indicated that the wording of the manipulation in the N. F. was faulty, therefore another batch of 100 grammes, employing the official quantities, was made by taring a 250 c.c. Erlenmeyer flask, adding 175 c.c. of water heating on the hot plate until boiling and then adding the lime and sulphur previously mixed and boiling on the hot plate without stirring or further attention until the weight was reduced to 100 grammes, transferred to a 4 oz. cork stoppered bottle, allowed to stand until the next day, filtered and assayed.

The solution contained 29.162 grammes of total sulphur in 100 c.c.

Another lot made by the same method contained 29.593 grammes of total sulphur in 100 c.c. solution.

These figures indicate that if the solution is prepared in a flask the product will practically be of uniform strength.

It is true the N. F. does not state whether a flask or evaporating dish should be employed. The result of the failure to specifically state that a flask or similar vessel be used is shown by the analyses

to yield preparations of indefinite strength. If a large enough flask is not at hand, vessels which are deep should be employed, the object being to avoid too rapid evaporation of water, as the proper preparation of the product requires several hours.

In view of the above results the Committee on National Formulary should revise the wording of the directions for the preparation of Vlemminckx's solution, and thus insure a uniform product. Of course if thought necessary a standard could be fixed for the preparation and a method of assay appended.

I would take this opportunity to acknowledge my indebtedness to my assistant, J. H. Wiener, Ph.C., for assistance rendered in the preparation and analyses of some of the samples.

#### A NOTE ON THE VALUE OF PRESERVATIVES IN SYRUP OF IRON IODIDE.<sup>1</sup>

By GEORGE M. BERINGER.

In the U. S. P. 8th Revision, diluted hypophosphorous acid to the extent of 20 Cc. to 1000 Gm. has been added to this syrup as a preservative. Several of the foreign pharmacopœias have used organic acids for the same purpose, the Austrian Pharmacopœia directing 0.1 per cent. of citric acid, the Swiss Pharmacopœia 0.05 per cent. of citric acid, and the French Pharmacopœia 0.1 per cent. tartaric acid. The German Pharmacopœia, the British Pharmacopœia, the Danish Pharmacopœia, the Swedish Pharmacopœia, and the Italian Pharmacopœia do not direct any preservative, dependence being placed upon the use of sufficient sugar.

In order to test out the relative value of these preservatives, six samples of syrup of iron iodide were prepared on October 15, 1913. In all of these the official process and manipulation and percentage of iron salt and sugar were carefully followed. These samples were preserved in my laboratory and not exposed to direct sunlight for several months. On December 18th, their condition was observed and noted. Subsequently these samples were filed with Chairman Remington and preserved in his laboratory with the other pharmacopœial samples until a few days ago, when I obtained them for observation of the further changes that had

<sup>1</sup> Read at the meeting of the New Jersey Pharmaceutical Association, Lake Hopatcong, June 17, 1914.

taken place. In the tabulation below the appearance on these two dates of each sample is noted:

No. 1.—Proportions of the U. S. P. formula, but without any preservative. On December 18th this sample was slightly yellow. It is now of a pale green color and appears to be in perfect condition.

No. 2.—U. S. P. 8th formula without any variation. On December 18th this sample was very pale but perfectly clear. It was noted that the green color had gradually faded out and the sample was much lighter in color than when first prepared. This is in accordance with the observations on this formula that had been previously reported.

This sample is now of a light yellow color and there is evidence of some change in the sugar, the change that we have commonly considered as caramelizing which takes place in the presence of hypophosphorous acid to a moderate extent.

No. 3.—Proportions of the U. S. P. with the addition of 0.05 per cent. of tartaric acid. This sample, on December 18th, had assumed a distinct yellow color. It has now faded until it is almost colorless.

No. 4.—Proportions of the U. S. P. formula with 0.1 per cent. of tartaric acid. On December 18th this sample had retained the light green color about the same tint as when first prepared. It now shows no change and appears to be in perfect condition.

No. 5.—Proportions of the U. S. P. formula with the addition of 0.05 per cent. of citric acid. On December 18th this sample was of a very light green color and preservation appears to have been perfect. It now shows no further change.

No. 6.—Proportions of the U. S. P. formula with the addition of 0.1 per cent. of citric acid. On December 18th this sample had retained its original pale green color, and at this time preservation appears to have been perfect.

Conclusions.—If syrup of iron iodide is carefully made and with the proper amount of sugar, no preservative whatever is needed. However, to overcome the careless manipulation on the part of some druggists, it has been deemed advisable to add a preservative. Hypophosphorous acid has the advantage of a reducing value which is not possessed by the organic acid suggested for this purpose. It has, however, the disadvantage that in the strength directed it will act upon sugar in strong solutions and darken the syrup. This could be overcome by substituting glycerin for a portion of the sugar directed in the formula.

## PETROLATUM LIQUIDUM, U. S. P. VIII (PARAFFINUM LIQUIDUM), WHITE MINERAL OIL.

By S. L. HILTON.

The U. S. P. VIII provides that this substance shall conform to the following description:

A mixture of hydrocarbons, chiefly of the methane series, obtained by distilling off most of the higher and more volatile portions from petroleum and purifying the liquid residue.

A colorless, or very slightly yellowish, oily, transparent liquid without odor or taste, but giving off, when heated, a faint odor of petroleum.

Sp. gr. .870 to .940 at 25° C. Tests as to solubility, acid impurities, fixed oils or fats, either animal or vegetable, and readily carbonizable impurities.

It is proposed for the U. S. P. IX to change the official title to Paraffinum Liquidum. This seems to be wise and in conformity to modern standards. The description, allowing a very slight yellow color, is a mistake, as there is no difficulty in obtaining a colorless oil except the oils of this kind that are produced in this country. The new requirement which requires that it shall be free from fluorescence is proper and not unnecessarily exacting.

From a careful study of a number of samples of white mineral oil, obtained from various sources, the appended table shows that the official requirements can be met without much difficulty; it is further demonstrated that an oil that is usually above the sp. gr. .870 will show more or less paraffin when subjected to a temperature of — 4° C., yet in the table two samples, each of the sp. gr. of .875, remained perfectly clear after being subjected to this temperature for eight hours. It is therefore evident that in the process of purification chilling was not thorough or carried on for a sufficient length of time, and the final filtration was not performed at the same temperature. The desire to have as heavy oil as possible for internal administration, as recommended by Dr. Lane, of London, is no doubt accountable for such a large number of samples with a specific gravity lower than .875 becoming opaque or milky at this temperature.

With proper manipulation and care an oil of the sp. gr. .8755 should show no separation of paraffin on chilling. Some standard covering this point should be provided; that is, a minimum specific

gravity that will show no separation of paraffin when the oil is subjected to a temperature of at least  $0^{\circ}$  C.

None of the samples showed an admixture of fixed oils or fats, either animal or vegetable. The test is one that must be carefully applied, or an accident will follow. The neutralizing of the alkali with strong sulphuric acid, after digestion, is violent unless it is added very slowly.

The results of the sulphuric acid test are most interesting, showing almost every shade of brown, and in several cases the only layer became opaque and colored and not conforming to the requirements of the pharmacopœia or the standard as given in the British or German Pharmacopœias.

As to the internal administration of paraffin oil, a number of specialists of this city have used it for several years. The principal method followed by them is to administer from 15 to 50 Cc. at bedtime; in obstinate cases of constipation 15 Cc. administered about one hour before meals, so as to avoid interfering with the process of digestion. With these methods of administration good results have been produced. There are, however, many cases where complaints have been made that the oil will pass out of the intestinal tract involuntarily, very much to the discomfort of the patient, even when given in very small doses. This trouble seems to be more frequent with the administration of one of the popular brands of the market which shows a specific gravity of less than .860. To a certain extent this may account for the growing demand for heavier paraffin oils.

Paraffin oils of a specific gravity of .880 or more are rather more difficult of administration than those of .870 to .875; they adhere to the mouth very closely, and to some are disagreeable and suggestive of castor oil.

An oil aromatized or flavored with some essential oil or combination of oils seems to be growing in demand. I submit ten samples, all of which, no doubt, to some would be agreeable. Personally, peppermint seems to be the most pleasant and agreeable; cardamon a close second. No doubt, many would prefer spearmint, owing to the chewing-gum craze.

The flavoring of paraffin oils must be done with care. From 5 to 25 drops of an essential oil, according to which is used, will be found sufficient for 500 Cc. While this small amount may not give a predominant odor, it must be remembered that the dose administered,

## EXAMINATION OF WHITE MINERAL OILS.

Brand.	Price gal.	Color and taste.	Odor.	Sp. gr. 23° C.	Saponif. test.	H <sub>2</sub> SO <sub>4</sub> test.	Freezing test, -4°/C.
Amalie Gloria, Grade "A".....	\$0.85	Colorless and tasteless	None	.87893	Nil	V. P. B.	Slightly opaque
Amalie Gloria, Grade "B".....	.75	Colorless and tasteless	None	.86752	Nil	V. P. B.	Slightly opaque
Amalie Gloria, Grade "C".....	.65	Colorless and tasteless	None	.85884	Nil	V. P. B.	Clear
Amalie Russian, Grade "A".....	.53	Colorless and tasteless	None	.85953	Nil	Brown	Clear
Amalie Russian, Grade "B".....	.50	Slight fluorescence; slight petrolatum taste	None	.85992	Nil	Brown	Clear
Liquid Albolene.....	.40 pt.	Colorless and tasteless	None	.85979	Nil	Brown, oil layer colored	Clear
Zinkeisen, Russian.....	.90	Colorless and tasteless	None	.87088	Nil	Brown, oil layer	Quite milky
National Aniline Co., No. 2.....	.80	Colorless and tasteless	None	.87546	Nil	Brown	Clear
National Aniline Co., a2138.....	.80	Colorless and tasteless	None	.88154	Nil	Brown	Slightly opaque
S., K. & F. Co., Russian.....	.80	Colorless and tasteless	None	.87599	Nil	Pale brown	Clear
"Squibbs".....	.40 pt.	Colorless and tasteless	None	.87319	Nil	Pale brown	Slightly opaque
"Olo".....	.34 pt.	Yellow cinnamon	Slight cinnamon				
Terabolia.....	—	Fluorescent and tasteless	None	.87076	Nil	Brown, oil layer brown	Slightly opaque
Freeman's Russian Mineral Oil.....	.50 pt.	Colorless and tasteless	None	.85335	Nil	Red brown, oil layer dark brown and opaque	Slightly opaque
Petrolax.....	—	Colorless and tasteless	None	.88457	Nil	Pale brown	Quite milky,ropy separation in layer at top.
Unknown No. 1.....	—	Slight fluorescence	None	.88165	Nil	Dark brown	Clear
Unknown No. 2.....	—	Colorless and tasteless	None	.86812	Nil	Pale brown, oil layer slightly colored	Slightly opaque
White Liquid Vaseline.....	—	Very decided fluorescence	None	.87765	Nil	Red brown, oil layer dark brown, opaque	Quite milky
Barrett & Co., Russian.....	1.00	Colorless and tasteless	None	.85360	Nil	Pale brown	Quite milky
Wilson's Sons White Mineral Oil.....	.70	Sample dirty. Very yellow in color, no examination.		.8849	Nil		

## ABBREVIATIONS AND EXPLANATORY TERMS.

V. P. B. Very pale brown.  
Prices stated above are wholesale.  
Amalie brands, from L. Sonneborn Sons, Inc., New York.  
"Olo," American Olo Company, Llanerch, Pa.  
Terabolia, Robert C. Cadmus, Philadelphia, Pa.  
Freeman's Russian Mineral Oil, Aseptic Chemical Company, Chicago, Ill.  
Barrett & Co., Importers, Chicago.  
Zinkeisen, National Aniline and Chemical Company, E. R. Squibb & Sons, New York.  
S., K. & F. Co., Smith, Kline & French Co., Philadelphia, Pa.

15 to 60 Cc., will be sufficient to give a fairly pronounced taste. The samples submitted contain in each 500 Cc. the following amounts of essential oils: Almond, 15 drops; cloves, 10 drops; anethol, 10 drops; cinnamon, 5 drops; peppermint, 15 drops; spearmint, 15 drops; sweet birch, 25 drops; wintergreen, 25 drops; and aromatic, using the oils constituting spirit aromaticus comp., 15 drops.

Another interesting phase of the examination is the various prices charged for these paraffin oils, those with fancy coined names commanding very much more than other oils on the open market, and all, or nearly all, coming from the same source and possibly the same importer. As has been pointed out by Mr. Wilbert, the better or fine grades come from Russia, hence the name Russian Mineral Oil; the American oil usually has a fluorescence, slightly yellow in color, and a more pronounced petroleum odor when heated. The best grades of Russian oil can be purchased for about 80 cents a gallon, while those with trade or coined names will cost from 40 to 60 cents a pint.

The pharmacist should be, and is, able to supply physicians and his patients with an oil of high quality, reasonable in price, and should avail himself of the present opportunity. An oil of at least the sp. gr. .8750 that is colorless, tasteless, and free from fluorescence, that will not show more than a pale brown color with the sulphuric acid test, free from admixture with animal or vegetable oils, and remains clear when subjected to a temperature of 0° C. for four hours, seems to be the oil most desired and, if demanded, can readily be obtained.

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## THE PHYSIOLOGICAL CHARACTERISTICS OF ACETYLENE, WITH RESPECT TO ITS USE IN MINING.\*

By E. E. SMITH, Ph.D., M.D.

Like every other step in the progress of civilization, the use of acetylene involves certain readjustments of previous notions. In the art of illumination, these problems of adjustment have been particularly definite and impelling. Thus, the pine knot did not give way to the candle, probably, without anxious consideration of the danger of spattering, soot making, and extinction by drafts. Many

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\* A paper read at a meeting of the International Acetylene Association, late in 1913, for a report of which the *Quarterly* is indebted to Secretary A. C. Morrison, 42d St., Building, New York. Reprinted from the *School of Mines Quarterly*, vol. xxxv., 1914, pp. 143-153.

years of careful study were needed to solve the last of the dangers involved in the use of kerosene, while the difficulties connected with illuminating gas and electricity are still with us. This paper will be limited to the problems of adjustment presented by the use of acetylene as an illuminant.

This leads us at once to the inquiry, Is acetylene a direct poison? The answer is no. This question is asked with some seriousness, however, because, on the one hand, of the notoriously toxic action of common illuminating gas, due to the carbon monoxide which enters so largely into its composition, by reason of which the mind of the inquirer is already not only prepared to believe that acetylene is poisonous, but, in fact, in some instances has that idea rigidly implanted there. It is further asked with seriousness, because, in the literature of the subject, we find some views that it is poisonous. Early writers declared that it combined with the blood and had a marked poisonous effect, like carbon monoxide.

Any gas, when it replaces air, if incapable of supporting respiration, is injurious and even fatal, not because it is poisonous but because it deprives the body of oxygen. Because of this, acetylene is capable of doing injury. If it accumulates in some small, unventilated space, like the cabin of a boat, it is entirely capable of shutting off the supply of air, of preventing respiration and hence causing harm and even death. It suffocates because it is incapable of supplying oxygen, without which man cannot live.

When acting in this way, acetylene is not a direct poison; it does not do anything to the body to injure it. It does harm only indirectly, by withholding air. The recognition, then, of injury by suffocation throws no light on our inquiry whether it is a direct poison. The presence of common illuminating gas in air, even to the amount of a fraction of a per cent., is distinctly injurious and may even be fatal, though such air contain an abundance of oxygen. The carbon monoxide contained in illuminating gas enters the blood through the lungs and attaches itself strongly to the coloring matter of the blood, rendering it incapable of taking up the oxygen of air though the air contain oxygen in ample amount. Thus death supervenes not because the body is denied oxygen but because, through the fixation of the coloring matter of the blood, it has lost its capacity to use oxygen. Has acetylene this or any other directly poisonous action? Some early observers said it had. They found fixation of hæmoglobin quite similar to that of carbon monoxide



and accordingly declared acetylene a poison. Moreover, it seemed to exercise the action of a direct poison on animals.

This was ascertained before acetylene was regularly produced from carbide. The acetylene of that date was made by the incomplete combustion of coal-gas, whence more or less carbon monoxide was present in the acetylene obtained, thus accounting for some degree of toxic action of the acetylene examined. Carbon monoxide is the poison of common illuminating gas.

With the discovery of carbide and its use for the production of acetylene, all of this has been changed. It is now found that acetylene from carbide does not contain carbon monoxide, that it does not have the property of fixing hæmoglobin, and that it does not rob the blood of its capacity to take up oxygen from the air and carry it into the tissues. Hence the old allegation that acetylene is a poison because it deprives the blood of its oxygen-carrying capacity is no longer justified.

Another poisonous product sometimes present in the acetylene made by the old combustion process was hydrocyanic acid. Never in large quantities, it yet is so toxic that we can fully appreciate its effect. It is not present in the carbide acetylene and so may be dismissed from consideration. Another charge that is no longer justified is that acetylene is a poison because of the presence of phosphine as an impurity. This forms when carbide is made from limestone containing phosphate, which is reduced by the action of the coke. The selection of limestone free from phosphate has practically obviated this impurity and any poisonous effect of the acetylene consequent thereto. Indeed, the present day product may be said to avoid the pitfalls of impurities so that its effect is determined by the characteristics of acetylene itself. We may consider then whether acetylene, as such, is or is not a direct poison.

My present observations have been directed to the inquiry whether it produced noticeable effect on human subjects when present in increasing amounts up to  $2\frac{1}{2}$  per cent. during a period of  $2\frac{1}{2}$  hours. To this end, four men, including myself, were enclosed in a room of about 800 cu. ft. capacity; at the beginning and four times subsequently at intervals of a half-hour, acetylene was liberated in the room by throwing 450 grams of carbide into an open tub of water, this corresponding to the liberation of 4 cu. ft. of acetylene each time; that is, 20 cu. ft. in all,  $2\frac{1}{2}$  per cent. of the capacity of the room.

To eliminate, as far as possible, the mental effect of the environment, the subjects were engaged in playing a game of cards. They were interrupted only long enough to take readings of their blood pressures, at half-hour intervals. The results of the experiment were quite negative. The game was continued throughout the period, excepting as noted. The blood pressure remained constant with one subject and was very slightly lowered from the inactivity with two, and absolutely no effect was noted that could be ascribed to any poisonous or other action of the acetylene. It was without effect.

This same result has been obtained in experiments on animals. In such amounts as used in the above experiments there is no effect. Indeed, acetylene may be increased up to 20 per cent. and, if the mixture is so made as not to reduce the amount of oxygen, animals may be left in the atmosphere for some time, an hour or more, and will only become drowsy, from which they quickly recover when removed into ordinary air.

With very large quantities, or with 20 per cent. admixtures acting for a longer time, the degree of drowsiness is increased. That is to say, the effect of acetylene in large doses is that of a narcotic, producing loss of consciousness in proportion to its degree of action. When this action is pushed to a fatal termination, the final effect is upon the breathing centre, inhibiting its action and so producing death.

It thus appears that carbide acetylene is not poisonous in the sense that common illuminating gas is, and that in large quantities, acting for some time, it produces a narcotic action. In respect to its toxicity, it presents no problem of adjustment under ordinary conditions. It, of course, may not replace in large degree the atmosphere we breathe, but otherwise no poisonous action need be anticipated.

A number of interesting problems are presented in connection with the use of the acetylene lamp as an illuminant in mines. I do not refer to those conditions where explosive gases are present, where protection from explosions is obtained through the use of the Davy lamp in some of its modifications, but to that large number of mines which are regularly illuminated by the naked flame. For this purpose, the miner's oil lamp has been used for many years. It is light in weight, but its illuminating capacity is strikingly low and, moreover, is obtained at the expense of a smoking-out process that is amazing. It is a tribute to the miner's endurance that in the

past he has accomplished so much under the conditions of poor illumination and soot-laden atmosphere which the use of the oil lamp has meant. The use of the miner's acetylene lamp affords an illumination that is wonderfully efficient and entirely soot-free. Its use raises some questions that we may answer at this time. Before considering these, let us look at some of the problems which the miner has to face, upon which the choice of an illuminant may have some bearing. Of first importance is the composition of the air which he breathes.

For our present purpose we may regard the atmospheric air as a mixture of 21 parts of oxygen and 79 parts of inert gas, mostly nitrogen. It is the oxygen that supports life. The proportion of oxygen may be diminished to a certain extent without noticeable effect, especially if the difference is made up by inert nitrogen. Under these conditions a reduction to 14 per cent. produces little or no physiological effect. When the reduction reaches 12 per cent., there is apt to be slightly deeper breathing, while 10 per cent. is an amount distinctly below what is physiologically advisable. Seven per cent. may be regarded as the fatal point. It is an amount too small to support the life of animal or man for any considerable time. It must be kept in mind that these figures, 10 per cent. the physiological insufficiency and 7 per cent. the fatal point, are for oxygen with inert nitrogen, and without the admixture of poisonous gases.

There is always present in atmospheric air a small amount of carbon dioxide gas, commonly known as carbonic acid. This amount is very small, ordinarily not over 5 parts in 10,000. It is a product of the combustion of organic matter and is present in air exhaled from the body in breathing. As we shall see later, it is also a constituent of mine gases and so is of particular interest to us. I will call attention to what happens when it is added to the air.

To answer this question I have myself made direct observations. The apparatus employed was a closed cabinet, the inside measurements of which were approximately 67 x 30 x 69 in., having a capacity of 80 cu. ft. It was provided with a sliding door. Into the top a pipe entered and connected with three "sprays," one in each third of the top. Through this system gases were introduced. There was a small sample tube, easily movable, so that gas was withdrawn from any position desired within the cabinet, which was connected outside with (a) an exhaust bottle for withdrawing residual air

from the tube; and (b) a gas-sampling tube. Collections were made over mercury and analysis was made over mercury in a Hempel apparatus. The cabinet was tightly built, but not sufficiently so to prevent escape of air sufficient to equalize the pressure without and within the cabinet when gas was introduced. A movable electric fan within the cabinet was adapted to produce motion of the air.

When carbon dioxide was mixed with atmospheric air, it was noted that such mixture produced an increased rate of respiration, even when the proportion of carbon dioxide was small. Rabbits and guinea-pigs showed a marked increase when as much as 4 to 5 per cent. of carbon dioxide was present. With increasing proportions respirations became deep and labored, frequently, as was observed in guinea-pigs, reaching a condition of diaphragmatic spasm. Loss of muscular power developed so that, with guinea-pigs, ability to support the body was lost when the carbon dioxide reached 20 to 25 per cent. These symptoms developed irrespective of whether lamps were burnt in the same atmosphere. With rabbits, when lamps were burning, loss of muscular power appeared with the same proportion of carbon dioxide as with guinea-pigs, but in a single observation made without lamps, the loss of power appeared when the carbon dioxide had reached 36 per cent. No effort was made to determine the percentage of carbon dioxide that would produce death, as it was believed that the proportion producing loss of muscular power represented the limit of possible tolerance. It may be noted, however, that in the experiment carried to 36 per cent. carbon dioxide, the rabbit quickly recovered, two guinea-pigs recovered somewhat slowly, and one guinea-pig died, when the animals were removed into fresh air. Thus it appears that even with guinea-pigs, the fatal carbon dioxide proportion is not much if any below 36 per cent., while the carbon dioxide warning point is not above 4 to 5 per cent.

To test the effect of carbon dioxide on man, 10½ cu. ft. of carbon dioxide were passed into the cabinet, when a young man entered, the door being opened for that purpose and quickly closed. After entering, the fan was started. The rate of respiration at once rose from 18 to 48, being deeper and labored. He almost immediately complained of feeling dizzy. At the end of 2½ min. there was a feeling of impending loss of consciousness. A sample of the air mixture was at once taken and at the end of 3 min. the man came out. His respiration quickly returned to normal, but his face was flushed and he complained for several hours of a slight frontal

headache. Analysis of the sample showed 7 per cent. of carbon dioxide. The experiment indicated that with man the warning point is reached below 7 per cent. of carbon dioxide.

Such experiments lead to the following general conclusions regarding the physiological effects of increasing proportions of carbon dioxide. There is increase in the rate of breathing which, with 3 per cent. dioxide, has become so marked that it gives unquestioned warning to the subject that some unusual condition of the air is rendering it unsuited for breathing. We may call this the physiological warning point for carbon dioxide. When the concentration reaches 8 to 10 per cent., the breathing is not only rapid but has become very labored, a condition termed dyspnea. Beyond 15 per cent., further concentration, instead of increasing respirations, decreases them and the animal becomes narcotized, quite as though a substance like chloroform had been administered. At a concentration beyond 35 per cent. the narcosis becomes fatal.

I have gone into the influence of oxygen decrease and of carbon dioxide increase on breathing and on life because these are conditions that may be presented by the air in mines. Moreover, the oil lamp has been relied upon to indicate to the miner whether or not the mine air is fit to breathe, air that sustains the flame being regarded as safe and air that extinguishes the flame as unsafe to breathe.

The disadvantages of the oil lamp are all too apparent. Its dingy light limits the working capacity of the miner, due to poor illumination. Aside from working capacity, the miner is not so well able to see the elements of danger presented by weakness in overhanging strata or structures. An even greater disadvantage is the production of soot by the flame. This both adds to the personal discomfort, already great, and also to the danger of dust explosions by addition of the soot to the dust-laden atmosphere. These conditions render an illuminant that is brilliant and soot-free a very great advantage. The acetylene lamp supplies such an illuminant in an admirable manner. In connection with its use it is desirable to determine its relation to composition of mine air, so that the miner may know in what way and to what extent it replaces the oil lamp as an index of safety. That is to say, we have here a problem of adjustment to which it is important to give a correct and definite answer.

First, then, let us consider the variations in composition that may be presented by mine air. Because of the limitations of access of outside air and especially because of the formation of gases in

mines, mine air may present a considerable departure from the composition of outside air.

All ordinary foreign gases were known to the early miners as "damps," from the German *dampf*, meaning vapor, the specific designation being indicated by an individual prefix. Thus, the gas characterized by its tendency to extinguish the flame was called black-damp, or, since it tends to produce suffocation, choke-damp; the damp producing increased brilliancy of light, white-damp; that with a marked stink, stink-damp; that which readily took fire, fire-damp; the gas resulting from burning or explosion, after-damp, etc. These names were applied long before the composition of the respective gases was known. In consequence of the indefinite basis of the classification, an individual name was in many instances applied to mixtures that presented wide variation in composition.

Black-damp, on chemical analysis, has ordinarily proved to be a mixture of carbon dioxide and nitrogen, the proportion of carbon dioxide varying from very little up to 15 per cent. or perhaps exceptionally 20 per cent. As it is always mixed with more or less air, a corresponding amount of oxygen is present. Other gases, such as methane (fire-damp), carbon monoxide (white-damp), hydrogen-sulphide (stink-damp), also water vapor, may be present in greater or less amount.

We may well ask, then, what the name black-damp indicates. Does it mean carbon dioxide, which is the characteristic constituent; does it mean the carbon dioxide-nitrogen mixture; is it the carbon dioxide-nitrogen-air mixture; or is it the combination of any of these with other gases that are present in the mine air? Unfortunately, there has been no unanimity of usage in regard to this term, it having been used by different writers in almost every one of the above possible meanings.

If we were to establish anew the definition of the term, it would be doubtless wise to adopt a scientific meaning. As the matter stands, our meaning should be decided by priority, which is that black-damp is not simply carbon dioxide but rather a mixture of that with nitrogen in varying proportions, but we must not forget the different usages of individual authors.

Our problem is: How does the admixture of black-damp modify the respirability of mine air and how is this indicated by the oil and acetylene flames? It requires no facts other than those now before us to appreciate that it affects respirability in two ways. It dimin-

ishes the proportion of oxygen which, if reduced to 10 per cent., would be unphysiological and to 7 per cent., fatal; and it increases carbon dioxide which, when present to the amount of 3 to 4 per cent., would produce marked increase in the rate of breathing.

As to when the change in composition, especially the carbon dioxide increase, is indicated by the particular flames, has been the subject of personal experimental observations. The cabinet employed in the experiment previously described was used. In the earlier experiments with carbon dioxide, this gas was fed into the cabinet without previous admixture with air; in the later ones both air and carbon dioxide were fed into the cabinet through meters, entering the cabinet through a common tube. Thus they were well mixed and the rate of flow of each was regulated. Early experiments indicated that various factors influenced the extinction point, both for the oil and acetylene lamp. Let me relate what these factors were and how they exercised their influence.

*A. Acetylene Gas Pressure.*—From the outset it was observed that the pressure under which the acetylene gas was fed through the burner exercised a marked influence upon the extinction point. That is to say, with a series of lamps in which the acetylene gas pressure varied, as indicated by the character of the flame, it was not difficult, in a mixture of increasing proportion of carbon dioxide, to foretell the order in which the lamps would be extinguished, the lamps with higher acetylene pressure going out first. Indeed, it was frequently observed, where the escape of gas from the burner was under such slight pressure as not to give direction to the flame, that the extinction point would be very much higher than was observed with the ordinary burning flame. Care was therefore exercised to make our observations on lamps in which the gas production showed a normal amount of pressure.

*B. Air Movement.*—When there was no movement of air, excepting such as resulted from the convection currents produced by the lamps and by the introduction of the gas mixture, the extinction points were: for the acetylene lamps, 23 to 25 per cent. carbon dioxide; for the oil lamps, 12 to 14 per cent. carbon dioxide. With the production of a gentle movement of the air by fanning against the side of the cabinet, the extinction points were appreciably affected, being lowered in the case of the acetylene lamps to 22 to 17 per cent. carbon dioxide; in the case of oil lamps to 12 to 10 per cent. carbon dioxide.

With the production of a strong movement of the air, by direct fanning of the lamps, in two experiments the acetylene lamps were extinguished when the air contained 9.4 per cent. and 9.9 per cent. carbon dioxide, respectively, while the oil lamps were extinguished by the same breeze in atmospheric air.

The movement of the lamps worn on the heads of the miners would produce, in quiet air, the effects that result from a breeze with the lamps stationary. We may conclude, therefore, that in the case of the acetylene lamp the extinction point is lower than 25 per cent., in proportion to the rapidity of motion; and with the oil lamps, correspondingly lower than 14 per cent.

*C. Oxygen Proportion.*—In the experiments mentioned, the oxygen was reduced only moderately by the admixture of the carbon dioxide in the form of pure gas. Undoubtedly, such reduction tends to lower the carbon dioxide extinction point. The effect, however, is only moderate, since the oxygen in all experiments was distinctly more than would sustain the flame if the specific effect of the carbon dioxide were neglected.

When the admixture of carbon dioxide is in the form of black-damp, however, the question of the oxygen proportion becomes an important factor for consideration. In these preliminary investigations, we were not able to study the effect of black-damp, since with the use of so large a cabinet, the quantity of nitrogen required would be much greater than it was practical to obtain.

*D. Humidity.*—In a number of experiments, water vapor was introduced into the gas mixture by blowing over the surface of water within the cabinet. In this way, the humidity was raised from approximately 35 to 65 or 80. Any effect upon flame extinction by carbon dioxide that may have resulted was within the limits of variation from the other factors considered. The conclusion is therefore reached that humidity affects the proportion of carbon dioxide required to produce flame extinction only within relatively narrow limits.

Comparing now the effects of carbon dioxide increase on flame extinction and respiration, we note that the first effect is a physiological one, when the proportion reaches 3 to 4 per cent., there being an increase in the respiratory rate that is entirely adequate to warn persons of the atmospheric condition. Flame extinction occurs with oil at 13 per cent. and acetylene at 26 per cent. in still atmosphere, but at 10 per cent. and 17 per cent. with moderate motion. With



either lamp the extinction point is too high above the physiological warning point to make it of value to the miner. The conditions will have been recognized before the extinction point is reached. Should, however, the physiological warning be unheeded, flame extinction will occur, first with the oil and then with the acetylene flame, with either in ample time to prevent loss of life. The margin of safety, though greater with the oil lamp, is adequate with the acetylene.

In considering the influence of oxygen decrease on flame extinction, I shall make use of observations made by Chester S. Heath, under experimental conditions different from those I have described.

He finds that with moderate motion an oil flame is extinguished when the oxygen is reduced to 16.5 per cent.; in still air to 16.2 per cent. With acetylene, at moderate motion, extinction occurred at 12.6 per cent. and was dimmed in still air of the same composition, being extinguished in still air at 11.5 per cent. It thus appears that the oil flame is extinguished with considerably less reduction of oxygen than the acetylene, but that the latter is extinguished before the reduction is fatal to man, which is at 7 per cent. Moreover, in actual mining conditions, where the lamp is worn on the head, there will be sufficient motion; hence extinction will occur at a point somewhere above that observed with the experimental conditions.

Finally, it is not to be forgotten that the condition of extreme oxygen reduction without carbon dioxide increase, which was present in the experimental observations, is not encountered in actual mine air. The specific action of carbon dioxide admixture, that will be found in such conditions, will add its effect to the oxygen decrease and bring about the extinction of an acetylene flame at a point which is still further removed from unphysiological atmospheric conditions, and hence afford an increased margin of safety.

The miner, then, may conclude that a given admixture of black-damp and air in the absence of other foreign gases will support life: (1) if it does not extinguish flame; (2) if it does not produce markedly increased respiration. Any atmosphere which does not give these warnings is respirable, though not necessarily desirable for continuous respiration. It does, however, give warning either physiological, or by the flame of acetylene as well as oil, that is adequate to prevent loss of life.

THE 65TH ANNUAL SESSION OF THE AMERICAN  
MEDICAL ASSOCIATION.

By M. I. WILBERT, Washington, D. C.

The 1913 meeting of the American Medical Association was held in Atlantic City, June 22-26, and was attended by 3958 members who took the time and trouble to register. The registration this year is reported to have been considerably larger than that of any of the previous sessions of the Association in Atlantic City. The work of the House of Delegates and its committees and the proceedings of the several sections of the Association are reported at length in the *Journal of the American Medical Association* for July 4, 1914, vol. 63, pp. 73-130. The scientific papers, because of the restrictions imposed by the House of Delegates at the Minneapolis meeting, were fewer in number than in former years, but the subject matter discussed was correspondingly good, the programs for the several sections being generally well carried out.

The Section on Pharmacology and Therapeutics had, as usual, a program containing many papers of pharmaceutical interest. Delegates from the American Pharmaceutical Association were recognized, and Prof. Joseph P. Remington, the chairman of this delegation, in extending the felicitations of the organization he represented, said:

"The American Pharmaceutical Association brings greetings to the American Medical Association. It is meet and proper that two national bodies should exchange greetings, for, however they may differ in function and scope, they are united in principle in the one great object of promoting the health of the nation in combating disease.

"It is gratifying to know that the Pharmacopœia is practically completed, so far as the bulk of the work is concerned. The printing of the Appendix, with the Tables, Reagents, and Volumetric Solutions, will be sent to the printer this week, for this part of the book must be printed first, in order that members may have it for reference in checking up the text of the book.

"During the past year a number of older remedies have been deleted and new remedies admitted. A Committee on Scope which reports upon proposed admissions and deletions have finished their work, but there are still a few questions which can be settled after

the printing is started. One of these questions is the form of so-called bichloride tablets. As is well known, the enormous use of these tablets is a menace to the future growth and prosperity of the nation. The Pharmacopœia cannot check the use of these tablets, but it can at least direct the form for their use which will prevent accident so far as possible through swallowing the tablets or their solution.

"The American Pharmaceutical Association, during the past year, has used its influence in every possible way in controlling or limiting the use of habit-forming drugs by national and State legislation. Committees have been formed from the membership who are working to stamp out this evil.

"The body which I have the honor to represent asks the assistance of your body to aid in framing wise laws which will make it difficult for dopesters to continue their habits, and by limiting the use of these drugs to prescriptions by properly educated physicians, who are earnestly trying to curtail the evil.

"In educational matters Pharmacy has progressed in the direction of raising the standard of education of those entering Pharmacy, and enlarging the curriculum in the colleges. May we not hope that Medicine and Pharmacy will be more closely linked in the future, and that crimination and recrimination will cease, or take the form of constructive criticism, with the intention of remedying the evils and correcting abuses, and will be actuated by harmony between the two professions."

Referring more particularly to the probable scope of the U. S. P. IX, the following table represents the status of that book at the present time:

Number of articles in text of U. S. P. VIII.....	958
U. S. P. VIII articles dismissed from U. S. P. IX list.....	237
Number of articles retained from U. S. P. VIII.....	721
Number of new articles admitted to U. S. P. IX.....	67

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Total number of articles in tentative list of U. S. P. IX..... 788

On motion of Dr. Murray Galt Motter, of Washington, D. C., the Section on Pharmacology and Therapeutics of the American Medical Association adopted the following resolution, which was referred to the House of Delegates, endorsed by that body, and thus officially recognized as the opinion of the American Medical Association:

"WHEREAS, The Pharmacopœia of the United States of America should be, above all, a book designed to protect the public health and prevent the exploitation of the sick and afflicted for profit; now, therefore, be it

"*Resolved*, That the members of the Section on Pharmacology and Therapeutics of the American Medical Association request the House of Delegates to urge upon the Revision Committee to make official in the Pharmacopœia of the United States 'corrosive mercuric chloride pastilles,' so that physicians may not be compelled to prescribe this remedy under a proprietary name. Be it further

"*Resolved*, That this section endorse the form and description of corrosive mercuric chloride pastilles as described in the German Pharmacopœia, namely, of cylindrical shape, twice as long as thick, wrapped individually in paper bearing the name of the medicament, 'corrosive mercuric chloride pastilles,' and the word 'poison' in suitable and striking letters. Be it further

"*Resolved*, That a copy of this resolution be forwarded by the Secretary of the American Medical Association to the President and to each of the officers of the United States Pharmacopœial Convention, and also to the Chairman and to each member of the Committee of Revision of the Pharmacopœia of the United States."

Of the many papers presented in the Section on Pharmacology and Therapeutics, the following contributions were of more immediate interest to pharmacy:

Dr. John F. Anderson, the chairman of the Section on Pharmacology and Therapeutics, in his address discussed some unhealthy tendencies in therapeutics and referred more particularly to the ill-advised use of certain biologic products, such as the Friedmann vaccine for tuberculosis and crotalin in the treatment of epilepsy. In summing up this paper he suggested that, while advances in therapeutics are necessary and clinical trials must be made, these trials should be with adequate controls of otherwise treated cases and under circumstances in which every stage can be watched and the various clinical and laboratory observations be made a matter of unbiased record, and the best interests of the patients thus safeguarded. It is difficult to secure these conditions outside of a well-equipped hospital. Until a new method of treatment has received abundant confirmation of this sort it is unjust—to use no stronger word—to apply it promiscuously to patients who are not under constant observation and are not amenable to instant emergency relief.

In a paper on "The Medical Treatment of Chronic Intestinal Stasis," W. A. Bastedo, of New York, discussed the uses and limitations of many of the aperients and cathartics. In commenting on the now widely used paraffin oil, he called attention to a series of ten samples not one of which complied strictly with the requirements of the Pharmacopœia, and also stated that in writing prescriptions for paraffin oil or liquid petrolatum it is unfortunately true that it is practically necessary to specify some established brand, as the material supplied in retail drug stores very seldom, if ever, complies with the requirements of the Pharmacopœia or is of an otherwise satisfactory nature.

In a paper on active immunization in diphtheria by toxin-antitoxin mixtures, William H. Park, of New York, reported on recent progress in the prophylaxis of diphtheria and reviewed the present-day knowledge regarding immunization and the possible recognition of immunization by skin reaction.

In a paper on the use of diphtheria antitoxin in the treatment of diphtheria, Samuel S. Woody, of Philadelphia, recommended the administration of much larger doses than are used at present, and also asserted that the number of antitoxin units to be administered should be in keeping with the stage of the disease. He also stated that as a prophylactic diphtheria antitoxin was uncertain and in a great measure unsatisfactory in its results, and that to be efficacious in the treatment of diphtheria, antitoxin must be given at the earliest possible moment and in large doses.

In addition to the resolution endorsing the inclusion of pastilles of corrosive mercuric chloride in the Pharmacopœia of the United States, the House of Delegates also adopted the following recommendation of pharmaceutical interest suggested by the Council on Medical Education and endorsed by the reference committee:

"Your committee also recommends that the Council be instructed to urge all medical colleges to adopt the nomenclature of the Pharmacopœia of 1910, and to use the metric system in their teaching."

The scientific exhibit was of unusual interest, and the work displayed was not alone excellent, but much of it was of immediate practical value to the profession. The commercial exhibit attracted considerable attention and was unusually free from objectionable features in the way of proprietary and semi-proprietary preparations not recognized by the Council on Pharmacy and Chemistry.

The officials for the Section on Pharmacology and Therapeutics

for the coming year are: Chairman, R. A. Hatcher; vice-chairman, J. Ray Arneil; secretary, M. I. Wilbert; delegate, John F. Anderson, and alternate, Ray L. Wilbur.

At the opening meeting of the Association on Tuesday morning Dr. Victor C. Vaughan, of Ann Arbor, Mich., was installed as president, and at the concluding session of the House of Delegates on Thursday afternoon Dr. Wm. L. Rodman, of Philadelphia, was selected as the president-elect and San Francisco chosen as the place of meeting for 1915.

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### BOOK REVIEWS.

DIGEST OF COMMENTS ON THE PHARMACOPOEIA OF THE UNITED STATES OF AMERICA AND ON THE NATIONAL FORMULARY FOR THE YEAR ENDING DECEMBER 31, 1912. By M. I. Wilbert and M. G. Motter.

One hardly realizes the vast amount of writing done annually in reference to pharmacopœial matters until one peruses the above useful compilation and the several that preceded it.

We do not say that Charles Rice "built better than he knew," because he knew many things, if all we have learned of him is true, but he certainly built wisely and with the foresight possessed by a great mind when he suggested and carried out the idea of compilation and classification of critical references anent matters pharmaceutical. That we live in a day and under a form of government that sees its way clear to carry this idea to fuller fruition augurs well for pharmacy in this country.

JOHN K. THUM.

ANNUAL REPORT OF THE INVESTIGATIONS CARRIED OUT UNDER THE SUPERVISION OF THE THERAPEUTIC RESEARCH COMMITTEE OF THE COUNCIL ON PHARMACY AND CHEMISTRY OF THE AMERICAN MEDICAL ASSOCIATION, VOLUME II, 1913.

This small volume of 111 pages embodies the results of some practical research work that is bound to have an influence for good on medicine and pharmacy. Both physicians and pharmacists would do well to purchase this little volume, which can be obtained for a small sum, for it will put them in possession of some positive knowledge on the possibilities and limitations of some well-known drugs. While it may be true, as is sometimes said, that medicine is not an

"exact science," yet if it is ever to be raised from the slough of empiricism, work of this kind *must* be done and persistently promulgated among the members of the professions.

JOHN K. THUM.

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## PHILADELPHIA COLLEGE OF PHARMACY.

### QUARTERLY MEETING.

The quarterly meeting of the Philadelphia College of Pharmacy was held June 29, 1914, at 4 P.M., in the Library; the President, Howard B. French, in the chair. Fifteen members were present. The minutes of the annual meeting, held March 30, 1914, were read and approved.

The minutes of the Board of Trustees for March, April, and May were read by the Registrar, J. S. Beetem, and approved. The report of the Committee on Necrology was read by the Chairman, and referred for publication in the AMERICAN JOURNAL OF PHARMACY.

Professor Stroup reported verbally for the delegates to the Pennsylvania Pharmaceutical Association. The attendance was somewhat smaller than usual. The reception of delegates from other organizations and reports of delegates to other bodies were the features of the first day's session. A large number of papers were, as usual, presented, the one on "Bacterial Vaccines and Serums," by Dr. A. P. Hitchens, being most interesting. The report of the Legislative Committee and the report of the Secretary of the State Pharmaceutical Board were also presented. The president, R. H. Lackey, made a number of recommendations which, after being referred to a special committee, were adopted. The Association elected the former secretary, E. F. Heffner, president, and David J. Reese, secretary. The next meeting is to be held at Forest Park, Pike County.

The delegates to the Delaware Pharmaceutical Association reported verbally by its chairman, Dr. A. W. Miller. The meeting was held at Hotel Du Pont, Wilmington, on June 4th. The reports of the officers and committees occupied the morning session. The meeting was not a very large one, but a very harmonious one. Your delegate was accorded a cordial welcome, who urged upon the members their help to influence congressional action in securing a

site for the statue to Professor Procter in front of the Smithsonian Institution.

The delegates to the New Jersey Pharmaceutical Association reported through the chairman, George M. Beringer. The 44th annual meeting was held at Hotel Breslin, Lake Hopatcong, June 16th to 19th. The absence of other members of the delegation, owing to the commencement exercises of the College occurring at the same time, was very much regretted. The meeting was one of the largest attended and most interesting sessions ever held. The sessions were well attended, and under the able executive the business was thoroughly yet expeditiously considered. Legislative matters were again one of the principal topics considered and the incoming Legislative Committee was instructed to have the proposed new pharmacy law, with a prerequisite clause, again presented to the next Legislature, and to use their best endeavors to have this bill enacted. The Committee on Papers and Queries presented an unusually interesting report. About twenty papers were read and discussed. A number of these were contributions from the members of this College. The subjects covered a wide range: commercial, educational, legal, scientific, and practical pharmaceutical questions were treated in these papers. Of no less interest were the discussions they provoked. The internal affairs and finances of the Association were subjects for earnest consideration. The President, in his annual address, advocated an increase in the dues in order to avoid a deficiency. Mr. John C. Gallagher, of Jersey City, was elected president, and Mr. G. M. Hays Deemer, of Atlantic City, was elected vice-president. The entertainments provided by the Local Committee and Travelling Men's Auxiliary were good and sufficient for the occasion without infracting upon the time needed for business.

Professor Kraemer presented the following resolution referring to a celebration of the fiftieth anniversary of the founding of the Alumni Association:

"As the session of 1914-15 will mark fifty years since the Alumni Association of the Philadelphia College of Pharmacy was established, and as the founders rendered yeoman service in the development of the educational facilities of the College, *Resolved*, That the College recognize this interest in her former students and arrange for a fitting celebration to commemorate this milestone in the history of the Association."

The reading of the paper caused considerable discussion. Mr.



French said that the Alumni Association had been foremost in all the advances the College had made, either as the originator or supporter of these advanced movements. The discussion was further participated in by Messrs. Beringer, Kraemer, Poley, French, Miller, and Stroup, when Mr. Beringer moved that a joint committee of the Board of Trustees and the Alumni Association be appointed to consider the matter. Adopted.

Professor Kraemer presented a framed receipt for two hundred dollars, contributed by the Class of 1889 for the Centenary Fund now in process of collection. On motion, it was voted to place it in the Library.

Professor Kraemer referred to the work which had been done during the past fifteen years, prior to the establishment of the present course in Bacteriology, and requested that a succinct account of the work be compiled from the reports of the Committees on Instruction and Examination.

Mr. Beringer, in commenting on the paper just read, said he wanted to call particular attention to the advances the College has made in its courses of instruction. There should be still further advances made. We should have post-graduate courses. No other college is giving the advanced courses that we are giving, especially in Pharmacognosy. More publicity should be given to the instruction given in the College. Our third-year class should be augmented from graduates of other institutions who are receiving less than we are giving.

The President made the following appointments:

Committee on Nominations: W. A. Runsey, E. F. Cook, W. L. Cliffe, Otto Kraus, John K. Thum.

Committee on Necrology: Henry Kraemer, Joseph W. England, C. A. Weidemann.

C. A. WEIDEMANN, M.D.,  
*Recording Secretary.*

## ABSTRACTS FROM MINUTES OF THE BOARD OF TRUSTEES.

*March 3, 1914.*—Thirteen members present.

Committee on Property reported that a lunch room had been opened, that the lunches furnished were of good quality, and that

the number of student patrons was greater than had been expected. The caterer expressed his satisfaction at the results of the undertaking, and it was regarded a success. The committee suggested the advisability of larger accommodations for the next session. The committee also reported complaints having been made concerning students smoking throughout the building, and advocated the enforcement of more stringent rules governing this practice, confining smoking to the cemented portions of the first floor and basement.

Committee on Library reported 398 books accessioned during the month, making a total of 6676 books ready for cataloging. Two hundred and forty-one persons had used the Library.

Committee on Examinations presented the results of the recent examinations held at the end of the first semester for the classes of the first, second, and third years.

Committee on By-laws proposed several amendments: To amend Article 8, Section 3. To amend Article 11, making same Article 12, and to introduce a new Article on Scholarships and Fellowships, as Article 11. Action was deferred until the next meeting.

Committee on Athletics presented a communication from the students representing the track team. The committee felt that the matter of athletics was one to be assumed by the Alumni Association and to be under their control and support. The subject was referred to the President of the Alumni Association.

Committee on Membership reported favorably on the application of Miss Agnes Duvoisin; a ballot was taken and she was unanimously elected to active membership.

*April 7, 1914.*—Thirteen members present. A communication was received from the Recording Secretary of the College, announcing the election of officers for the ensuing year and three Trustees for three years (see this *JOURNAL*, p. 229).

Nominations for officers of the Board being in order, George M. Beringer was elected chairman; Walter A. Rumsey, vice-chairman, and Jacob S. Beetem, registrar.

The Chairman read a communication from the staff of the "Graduate" 1913, offering to present a loving cup to be awarded to the first-year class 1914, and competed for thereafter under the rules governing the award of the President's Cup. On motion the offer was accepted and the appreciation of the Board expressed.

Dr. A. W. Miller read a communication from Professor Ernest Gilg acknowledging receipt of his Certificate of Honorary Member-

ship, for which he expressed appreciation and offered the College a set of his books. The offer was accepted with the thanks of the Board.

The Chairman announced the Standing Committees for the ensuing year, as follows: Property, Howard B. French, chairman; Library, Samuel P. Sadtler, chairman; Museum and Herbarium, O. W. Osterlund, chairman; Finance, Howard B. French, chairman; Supplies, H. K. Mulford, chairman; Accounts and Audits, C. A. Weidemann, chairman; Instruction, George M. Beringer, chairman; Scholarships, Joseph P. Remington, chairman; Examinations, William L. Cliffe, chairman; Theses, Joseph W. England, chairman; Discipline, Howard B. French, chairman; Announcement, Samuel P. Sadtler, chairman; Commencement, Walter A. Rumsey, chairman; Alumni, Joseph W. England, chairman; Appropriations, composed of chairmen of all committees empowered to make expenditures, also the chairman of the Board of Trustees, the chairman of the Committee on Finance, and the Treasurer.

Mr. French presented souvenirs, consisting of invitations, programs, menus, advertisements, etc., relating to past affairs of the College. These were of historic interest and were referred to the Historical Committee.

Professor Remington referred to the Panama Exhibition in 1915, expressing the thought that it would be to the advantage of the College to exhibit a line of official and N. F. preparations, together with historical matter, and suggested that a committee be appointed to make arrangements and that the College make an early application for space. On motion it was voted that a committee of five be appointed.

*April 21, 1914.*—Eleven members were present.

Committee on Examinations reported favorably on the application of Prof. Edwin Leigh Newcomb, P.D., for the degree of Master in Pharmacy in course, all the requirements having been complied with. A ballot was ordered and the applicant was unanimously elected to receive the degree at the next commencement.

Committee on Instruction reported that they had held a number of meetings to consider the annual reports from the Faculty. Abstracts from these reports are as follows:

*Department of Pharmacy:* The record of attendance as now made obligatory has been of special value. The extra lectures on pharmaceutical subjects have been attended by a much larger number of

students than heretofore; the increased time given to this department has permitted considerable additional instruction in Operative Pharmacy. It is thought desirable that this department be furnished with a lantern for illustrating lectures on prescriptions, etc. Numerous slides have been accumulated, and these are used to advantage, but they are not as effective as the projection of the actual prescription.

The course in Commercial Training has been greatly increased, and the former indifference of the students has given way to eagerness to absorb information.

The instructor in Latin reports that his work has been satisfactory.

*Department of Chemistry:* Professor Sadtler reports upon the work of the second- and third-year classes. By the lengthening of the College year, and the increase in the hours of instruction, a more extended course of instruction is given. In addition to the course of public lectures that have been given in recent years to the third-year classes, it is thought that a series of lectures for the second-year class could be introduced to considerable advantage. As the instruction to the second-year class covers many of the commercial chemicals, it would seem that a series of lectures bearing upon that subject would be especially beneficial.

*Department of Materia Medica:* Increased attention has been given to the physiological assaying of drugs with good results.

*Department of Botany and Pharmacognosy:* Advanced methods have been used. With each laboratory lesson a mimeographed outline of the work is given the students, printed on sheets of uniform size to fit in the notebooks used in this department. In the first year the initiative work is on the principal groups of plants, which is a little difficult for the beginner, and interest has been stimulated by periods of debates. A Biological Club has been organized; a program is arranged, and the discussions are illustrated with the lantern. In the second year the subject matter has been presented in groups according to their natural relationships. Two hundred and fifty-four types of drugs have been arranged in twelve-ounce jars, which have been consulted at recess and other times; the reviews have been of great help also. The third-year work has been in the study of chocolate products, spices, and a number of National Formulary drugs. Professor Kraemer, having been relieved of the teaching in Bacteriology, has been enabled to develop a special course in Microscopy

for the Special Chemical students. It is suggested that time be provided for compulsory botanical excursions to be considered as part of the laboratory exercises. The green-house and roof garden continue to be very serviceable in giving instruction.

*Department of Analytical Chemistry:* The instruction in this department has been carried on in accordance with the published announcement and outlined course. The results have been very satisfactory, and a continuance along the same lines is recommended.

*Department of Bacteriology:* The attendance at lectures was uniformly good. The laboratory instruction in the regular course will be doubled.

*Department of Physical Culture:* About two-thirds of the class presented themselves for examination. New record cards have been prepared. Many of the students were found to be under weight and flat-chested, and the proper gymnastic training for these conditions was given.

*Physical Director:* This report contains a number of interesting items on the work of the department.

May 5, 1914.—Eighteen members present.

Committee on Library reported 472 books shelf-listed, making a total of 7690 books ready to be catalogued. Use of Library for the month by 382 persons.

Committee on Supplies were given power to act in procuring additional microscopes.

Committee on Examinations reported having received a communication from the Secretary of the State Pharmaceutical Examining Board, requesting that the final result of the third-year examinations be recorded in time to comply with the State Board requirements.

President Howard B. French presented to the College, on behalf of Mrs. Mary I. Banks, a check for \$5000 with which to establish a fellowship in memory of her father, the late Clayton French. The following resolution was adopted:

*Resolved,* That the Board of Trustees of the Philadelphia College of Pharmacy gratefully acknowledge receipt of Five Thousand Dollars through the hands of Mr. Howard B. French from Mrs. Mary I. Banks, to be used in establishing a fellowship in honor of her father, the late Clayton French.

*Resolved*, That a tablet be erected in the hallway of the College bearing the following inscription:

1824

1890

Clayton French  
FELLOWSHIP

Established by his daughter

Mary I. Banks

May 16th, 1914

The Dean moved that the gift be accepted and that the grateful thanks of the College be expressed. It was further resolved that the income from the fund should be used for advanced research work.

Mr. Campbell referred to the N. A. R. D. Convention to be held in August in this city, and favored representation by the College. After discussion, a committee of five, consisting of Messrs. Campbell, Osterlund, Remington, Mulford, and Evans, was appointed to consider the matter and report to the Board.

The Chairman announced the appointment of the Special Committee on Panama Exposition: Joseph P. Remington, chairman; Joseph W. England, Warren H. Poley, H. K. Mulford, C. Stanley French; associates, Professors E. F. Cook, F. X. Moerk, Henry Kraemer. With authority to add to their number.

## OSAGE ORANGE, ITS VALUE AS A COMMERCIAL DYESTUFF.

It has long been known in the Southwest that the wood of the Osage orange tree contains a dyestuff that would give a more or less fast yellow color. An examination of the wood from Texas by F. W. Kressmann showed that it not only contains moric acid and morintannic acid, the same as fustic wood, but also that the dyeing principles are present in amount to be commercially valuable. A comparative series of dyeing experiments made with fustic and Osage orange wood and extracts showed the latter to be of equal value with fustic in regard to depth of colors produced, the amount of extract, the character of the dyeing, and fastness to light, weather, washing, etc.—*Science*, vol. xl, July 3, 1914, p. 37.

# THE AMERICAN JOURNAL OF PHARMACY

SEPTEMBER, 1914

## RHAMNUS PURSHIANA: ITS HISTORY, GROWTH, METHODS OF COLLECTION AND BIBLIOGRAPHY.

By C. W. JOHNSON and EDITH HINDMAN.

*Rhamnus Purshiana* was discovered in Montana, on the banks of a tributary of the Columbia River, in 1805 or 1806, by the members of the first North American transcontinental exploring expedition under the command of Lewis and Clark ("Silva of North America," by Sargent, vol. 2, 1895, pp. 37-40). It was also found by Lewis and Clark in what is now known as Oregon and Washington. On their return journey they took with them a specimen of the shrub for identification. The exact place where Lewis and Clark collected the type, later examined by Pursh, was Camp Chopunish, situated on the east bank of the Kooskooskee (Clearwater) River, about two miles below what is now known as Kamiah, Idaho (Contributions from the National Herbarium, vol. 11, "Flora of Washington," by Piper).

This plant, along with a number of other unknown botanical specimens collected on the journey, was given to Frederick Pursh, a German botanist, of Philadelphia, for botanical study. Frederick Pursh lived in America between the years 1799 and 1812. In 1812 he went to London, where, in 1814, he published a description of the plant, giving it the name of *Rhamnus alnifolia* ("Flora Americae Septentrionalis," vol. 1, 1814, p. 166).

Augustin Pyramus de Candolle (1778-1841) found that another plant had been named *Rhamnus alnifolia* by C. L. de Brutelle L'Heritier in 1775. In 1825 he changed the name of the plant described and named by Pursh as *Rhamnus alnifolia* to *Rhamnus Purshiana*, in honor of Pursh (de Candolle, "Prodromus Systematis Naturalis," vol. 2, 1825, p. 25).

The following is a translation of the Latin description of *Rhamnus*

*alnifolia* by L'Heritier, *Rhamnus alnifolia* by Pursh, and *Rhamnus Purshiana* by de Candolle, as copied in Latin by John Uri Lloyd from the original works in the Lloyd Library, Cincinnati, Ohio:.

*Rhamnus alnifolius* (L'Heritier, "Sertulum," p. 5), erect; leaves oval, serrulate, veins straight, pointed obliquely toward the end, under surface smooth, with flowers dioecious; peduncle one flowered, with calyx acute, fruit top shaped.

*Rhamnus alnifolius* (Pursh), *R. inermis* (unarmed or without thorns); leaves oval, denticulate, short acuminate; base cordate and slightly curved, veins underneath covered with hairs; peduncle split twice into two parts, berry globose but depressed. On the banks of the river Kooskooskee. Berries purple, very highly esteemed by the Indians of that country. (Pursh's "Flora Americæ Septentrionalis," vol. 1, 1814, p. 166.)

*Rhamnus Purshianus* (de Candolle), erect; leaves oval, denticulate, short acuminate, cordate and slightly curved, veins underneath covered with hairs, peduncle split twice into two parts, berry globose but depressed. On the banks of the river Kooskooskee. *Rhamnus alnifolius* (Pursh, "Flora," vol. 1, p. 166, not L'Heritier) ("Prodromus Systematis Naturalis Regni Vegetabilis," by de Candolle, vol. 2, 1825, p. 25).

Johann Friedrich (Iwan Iwanowitsch) Eschscholtz, a Russian naturalist, discovered the plant on the shores of San Francisco Bay, California, in 1816, and it was described by him in the "Memoirs of the Academy of St. Petersburg," vol. 10, 1826.

Prof. C. S. Sargent ("Notes on North America Trees," vol. 23; *Garden and Forest*, Feb. 18, p. 75; *The Pacific Druggist*, April 15, 1891) states that in 1838 Rafinesque describes in the "Silva Telluriana" his *Personon Laurifolium*, his description being drawn from a plant which he found in Bartram's Botanic Gardens, in Philadelphia. It is a tree, he says, from the Oregon mountains with elliptical, acute, sub-entire, shining, glabrous leaves pubescent on the lower surface when young, reniform petals, and slight emarginate stigma. The plant in Bartram's Gardens was twenty feet high, and the berries formed fine clusters and assumed three colors, being by turn green, red, and black when fully ripe. This is the earliest record of the cultivation of *Rhamnus Purshiana*, for there does not seem to be much doubt that it was this plant that Rafinesque had in mind. Certainly there is no other tree from the mountains of Oregon which could be made to answer to this description. If Lewis



and Clark, as is possible in the case of the plant of whose medicinal value they must have learned from the Indians, had brought home seed, these might very well have produced by 1838 trees twenty feet in height.



FIG. 1.—A Cascara tree on University of Washington campus.

*Rhamnus Purshiana* is claimed to have been known since the early part of the nineteenth century to the Mexicans and Spanish priests of Old California. It was known by the Spanish name of

Cascara Sagrada (sacred bark), so named because the wood was supposed to be identical with the "Shittim" or "Chittim" wood used in the building of the Ark of the Covenant.

COMMON NAMES.—In the different localities where it grew the tree was known by the Indians and early white settlers by the following names: Bearberry, Barberry, Coffee-berry, Coffee-tree, Bitterbark, Bear-wood, Wahoo, Shittim-wood, Chittim-wood, and Cascara Sagrada.

RANGE.—*Rhamnus Purshiana* is widely distributed throughout the Northwest. It is found in small quantities at the head of the Portland canal and mouth of the Unuk River in Southeastern Alaska and in northern British Columbia, in commercial quantities on the west slope of the Cascade Mountains of southern British Columbia, Washington, Oregon, and northern California.

It grows in the Mission Mountains and near the Flat-head Lake in Montana, in the Bitter-root Mountains and Seven-Devil Mountains in Idaho. It occurs occasionally on the eastern slope of the Sierra Nevada Mountains, and then reappears in the mountains of Colorado and western Texas. In one of its forms it is scattered throughout the mountainous regions of southern California, Arizona, New Mexico, and northern Mexico.

COMMERCIAL RANGE.—The tree grows abundantly and attains its greatest size on the western slope of the Cascade range of mountains in Washington, Oregon, northern California, and southern British Columbia. Plenty of moisture and a slightly sandy soil are favorable factors for its rapid development.

It is usually found in small river bottoms, sides and bottoms of canyons, growing under the shelter of coniferous forests, around the edges of swamps, and on slightly elevated moist areas.

With favorable soil and moisture the tree frequently springs up in places formerly covered with coniferous trees that have been destroyed by fire. It is seldom found in broad river bottoms or valleys on account of being crowded out by the more thrifty and rapid-growing alder and cottonwood trees.

The tree is found at sea level and up to an altitude of 1800 to 2000 feet. Men working in the cascara forests of Washington state that the tree grows to a height of twenty to thirty feet and attains an average diameter of six to eight inches. Trees having a diameter of three feet have been found. Sargent ("Silva of North America," vol. 2, p. 37) states that the tree attains a height of thirty-five to

forty feet with a diameter of eighteen to twenty inches. In shady places the tree grows tall, straight, and slender, while in open places with plenty of sunlight it branches near the base, attains greater diameter and less height.

A mild, moist climate is necessary for the abundant growth and large size of the tree. In a dry climate and higher altitude it occurs sparingly and in shrub form only. In its most northern range, in Southeastern Alaska, it also grows as a shrub of three to six feet in height. In certain sections of the California coast it has a height of only a few inches with prostrate stems.

REFORESTING.—Opinion differs as to the natural reforestation of cut-over areas. It is stated by some that a new growth always springs up on cut-over areas, providing the bark is not removed from the stumps; while others claim that sprouts rarely spring up from stumps, because the trees are usually cut while the sap is running, hence very little life is left in the stump.

The tree is a prolific seeder; seeds are of medium high germination (often tardy) and of very persistent vitality. Scattered seedlings are fairly abundant in moist forests, litter and mucky soils; scanty in drier habitat, except in depressions where seeds have been deeply covered by accident. (Geo. B. Sudworth, U. S. Department of Agriculture, Forest Service Bulletin, "Forest Trees of Pacific Slope," 1908, p. 404.)

LONGEVITY.—The longevity has not been fully determined for large trees. Trees ten years old are from six to eight inches in diameter. Trees estimated at twenty-five to forty years old are frequently found.

CULTIVATION.—For several years the U. S. Department of Agriculture has conducted experiments looking towards the cultivation of this tree, and has succeeded in growing it from the seed in moist places near Washington, D. C., the trees in six years from the seed attaining a height of ten to twelve feet.

The Kew Gardens in England ten years ago raised cascara sagrada from the seed collected in California, and it has proved quite hardy. The tree has also been grown in Germany, but is said to develop but slowly.

In the experiments conducted by the Department of Agriculture a certain method of pruning has been followed which forces the top of the tree into three or four branches; one of these branches may be cut each year for peeling, and, as another branch soon develops in its

place, this will be ready for cutting in a few years, the other branches in the meantime having been treated in the same way.

Seed of *Rhamnus Purshiana* is not on the market, but would have to be collected by some one in the cascara region. (Alice Henkel, "The Cultivation of Medicinal Plants," *The Druggists' Circular*, March, 1912, p. 133.)

The following is a description of the bark, leaves, flowers, and nutlets of *Rhamnus Purshiana* by Sargent ("Silva of North America," vol. 2, pp. 37-40).

The bark of the trunk, even on old trees, is rarely more than a quarter of an inch thick, and varies in color from dark brown to light brown or gray tinged with red, the surface being broken into short, thin scales. The branchlets, when they first appear, are coated with fine, soft pubescence; they are pale yellow, green, or reddish-brown, and are pubescent, glabrous, or covered with scattered hairs in their second season, when they are marked with large, elevated scars left by the falling of the leaves.

The leaves are alternate, elliptical-oblong, obovate, acuminate, or broadly elliptical, and are obtuse, acute, or bluntly pointed at the apex, rounded sub-cordate, or sometimes wedge shaped at the base, and serrulate, denticulate, obscurely crenate, or often merely entire with wavy margins. They are thin membranaceous or sometimes thick and coriaceous, and are glabrous or pubescent with scattered hair on the lower surface and along the veins on the upper surface. They vary from an inch to over seven inches in length, and are conspicuously netted veined, with broad and prominent mid-ribs and primary veins; they are borne on stout, often pubescent, petioles one-half inch or an inch long, and are sometimes pale yellow-green above and below, and sometimes dark green and rather opaque above and paler and often somewhat orange color or brown on the lower surface.

In Washington and Oregon and at high elevations in the mountains the leaves fall late in November, having previously turned pale yellow. Farther south and near the California coast they remain on the branches almost all winter, or until the following spring. The stipules are membranaceous, acuminate, and nearly deciduous.

The flowers are produced on the young shoots in axillary umbellate cymes or slender, pubescent peduncles varying from one-half to nearly an inch in length. The pedicels are slender, pubescent,

a quarter of an inch to almost an inch long and four to five times longer than the calyx, which is narrowly campanulate with more or less spreading acuminate lobes. The petals are minute, ovate,



FIG. 2.—Peeling Cascara bark in Washington forests. Illustrating a method employed in commercial collection, and the dense forest in which the collector must work.

and deeply emarginate at the apex, and enfold the short stamens, whose filaments are somewhat thickened at the base. The style is crowned with a slender two-lobed stigma. The fruit globose or broadly obovoid, a third to one-half inch in diameter and very

slightly or not at all lobed, with thin, rather juicy pulp and two or three nutlets. It is at first green, then red, and finally black at maturity.



FIG. 3.—Cutting Cascara tree in Washington forests.

The nutlets are obovate, usually a third to an inch long, rounded on the back, and flattened on the inner surface by mutual pressure, with two bony, tooth-like enlargements at the base, one on each side of the large scar of the hilum, and a thin gray or pale yellow-

green shell. The testa of the seed is thin and papery, its outer surface of a yellow-brown color and its inner surface like the cotyledons, bright orange color.

CHARACTERISTICS OF THE WOOD.—The wood of *Rhamnus Purshiana* while green is soft and brittle, but when dry it is tough and hard. After the bark is removed from the wood it checks very easily on drying. It is used to some extent in making ax-handles and wagon spokes.

COLLECTION OF BARK.—The season for peeling and collection of the bark is during the months of April to September. The tree is usually cut down and the bark removed from every part except the smallest branches. Trees of four inches or less in diameter are not cut, because the bark is too thin. Foreign material, such as sand, moss, etc., is removed by scraping; the common curry comb is the convenient tool. Those who peel on a small scale usually prepare very clean bark, while those who work on a larger scale are frequently careless in removing foreign matter. Much of the bark is collected by small ranchers and Indians living in the vicinity of the cascara areas. Larger quantities are collected by companies, who employ a number of men for this purpose during the season of collection.

CURING OF THE BARK.—After being mossed the bark is spread out on the ground on tarpaulins or on racks in the sunshine to cure. Sometimes it is kept under cover during the curing period. If placed in direct sunlight it usually takes about four days for the curing process. About 60 per cent. of its weight is lost during the curing stage. If not rained upon the bark will cure with a rich satin brown color, while if rained upon it will be spotted with black or become entirely black. Slow, careful drying yields bark 10 per cent. heavier than if hastily dried. The bark when dry is broken into small pieces, usually by means of a feed chopper, then packed into sacks holding from 50 to 100 pounds and stored in a dry place. The collector of the bark seldom keeps it during the aging period of one to two years. The season's collection is, as a rule, contracted for before peeling begins, and the product is shipped early in the fall. The dried bark must be carefully kept, otherwise it will absorb moisture and deteriorate.

PRICES AND PRODUCTION.—When first introduced to commerce the bark of cascara sagrada commanded a price of fifty to sixty cents per pound. The supply, however, rapidly increased and prices fell

during the next few years. The following table presents data on prices and annual production of the bark for the last decade, as compiled from the files of the *Oil, Paint and Drug Reporter* by Rodney H. True (*The Pharmaceutical Era*, January, 1913, p. 9) :

Year.	Highest price per pound.	Lowest price per pound.	Estimated quantity of bark peeled.
1901.....	5.5 cents	4.5 cents	500-600 tons.
1902.....	6.0 cents	4.75 cents	450 tons.
1903.....	22.5 cents	10.0 cents	1000 tons.
1904.....	17.00 cents	7.0 cents	750-1500 tons.
1905.....	7.0 cents	5.5 cents	850 tons.
1906.....	11.0 cents	5.5 cents	200 tons.
1907.....	10.5 cents	8.5 cents	250-600 tons.
1908.....	9.5 cents	6.5 cents	
1909.....	8.5 cents	7.0 cents	
1910.....	7.5 cents	7.0 cents	550-600 tons.
1911.....	9.0 cents	7.5 cents	1000-2000 tons.
1912.....	10.5 cents	8.0 cents	500 tons.

Stewart & Holmes Drug Company, of Seattle, Wash., states that the average price of the bark on the Pacific coast for 1913 was 5 cents per pound, and the yield was estimated at 1200 to 1500 tons. It is estimated that about 50 per cent. of the annual yield is exported to Europe, the remainder being shipped to eastern drug manufacturers of the United States.

**FUTURE SUPPLY.**—Cascara dealers have been predicting for more than a quarter of a century that the supply would soon be exhausted, but each year the yield is sufficient to meet the demand. The greater portion of the easily accessible trees have been cut, therefore the collectors must find new fields, which are naturally more remote from transportation.

Collectors usually leave standing trees under four inches in diameter, because of the thin bark, which insures reproduction on cut-over areas. The vast holdings of large timber companies contain thousands of tons of cascara, but they will not permit the peeling of these trees. This fact, together with the fact that new trees are growing on tracts that have been peeled once or twice before, insures a supply of bark for many years.

**DESCRIPTION OF THE CURED BARK.**—It is usually in flattened or transversely curved pieces, occasionally in quills two to ten centimetres long, and three centimetres in diameter, bark one to three millimetres thick; outer surface dark brown or brownish red, frequently completely covered with grayish or whitish lichens, several of



which are peculiar to this bark, and with small groups of brownish apothecia, longitudinally striate, turning red when moistened with solutions of the alkalis; fracture short, with projections of bast fibres in the inner bark, the medullary rays one or two cells wide, forming converging groups; in cross section this inner surface of the bark indistinctly crenate; odor distinct: taste bitter, slightly acid. (Dr. Henry Kraemer, "Botany and Pharmacognosy," 3rd Edition, p. 524.)



FIG. 4.—Packing Cascara bark to trail. Because of the underbrush and fallen timber horses cannot be used except on trails.

DESCRIPTION OF THE POWDERED BARK.—The powdered bark is light brown; bast fibres long, much thickened, lignified; stone cells very thick-walled, about  $50\ \mu$  in diameter, crystal fibres containing monoclinic crystals of calcium oxalate; calcium oxalate also in rosette aggregates or monoclinic prisms 5 to  $20\ \mu$  in diameter; starch grains spherical, about  $4\ \mu$  in diameter; parenchymatous cells with yellowish contents colored red with alkalis. (Dr. Henry Kraemer, "Botany and Pharmacognosy," 3rd Edition, p. 759.)

STRUCTURE OF THE BARK.—The bark as described by Prescott consists of three parts; namely, the corky layer, the middle bark, and the inner bark.

The corky layer consists of an outer epidermis of dark brown weathered cells, then several rows of cells filled with a dark red coloring matter, and in the more recent bark a row or two of cells containing chlorophyll.

The middle bark is made up of parenchymatous cells, which are filled with small starch grains. There are visible, also, in the transverse section, several groups of cubical crystals and in the longitudinal section groups of very thick-walled yellow cells.

The inner bark consists principally of yellow medullary rays.



FIG. 5.—Transporting Cascara bark on pack horses to wagon road.

separated by bast parenchyma, through which are scattered numerous yellow bast fibres. As seen in the longitudinal section, these fibres are frequently surrounded by small cubical crystals. (Parke, Davis and Company, "New Preparations," Feb. 5, 1879; "Proc. of Amer. Pharm. Assoc.," vol. 27, 1879, p. 262.)

MICROSCOPICAL EXAMINATION OF THE BARK.—The corky layer is about 0.045 mm. thick, and consists of eight or twelve rows, somewhat flattened, rather thick-walled, but not sclerotic cells. The parenchyma of the primary bark is tangentially elongated, partly of a collenchymatic character, free from secondary cork, and contains

scattered groups of roundish stone cells, with very thick walls, and accompanied by single rhombohedric crystals; the thin-walled parenchyma contains numerous groups of crystals. The inner bark consists of medullary rays composed of two or three rows of thin-walled, somewhat radially elongated cells, and of broader bast rays in which the parenchyma cells are coarsely dotted upon the radial and horizontal walls, and loosely united in a tangential direction; the sieve-tubes are larger, irregularly angular, and united, to the number of four or six, by means of coarsely porous sieve-plates, and on the radial sides marked with roundish sieve fields; the bast fibres form alternate groups of two or three rows, extending into few bast rays, and are surrounded by crystal cells. (Dr. J. Moeller, *Pharm. Centralhalle*, No. 28, 1882; "Proc. A. Ph. A.," vol. 31, 1883, p. 166.)

HISTORY OF RHAMNUS PURSHIANA IN THE MEDICAL PROFESSION.

—J. Winchell Forbes (*Practical Druggist*, Aug., 1910, p. 48) states that cascara bark was brought to the notice of the public in 1872 by a man named Donnelly, who learned of its virtues from the Catholic priests and Indians of Oregon and northern California. The priests called the tree "shittim wood," claiming that it was identical with that used in making the Holy Ark, and for this reason the bark was called cascara sagrada (sacred bark).

Under the direction of Mr. Forbes, Donnelly made a preparation of the bark by macerating it in cider vinegar for two weeks. This preparation was sold as a patent medicine under the name of "Donnelly's Discovery," which appears to have been the earliest commercial use of the bark.

In a paper contributed to "New Preparations" (Parke, Davis and Company, Oct. 15, 1877, p. 8), Dr. J. H. Bundy, an eclectic physician of Colusa, Cal., commended cascara sagrada as a valuable remedy in the treatment of constipation. In January, 1878, Dr. Bundy contributed a paper on the subject of cascara sagrada in which he gave the uses of its fluidextract.

To Dr. J. H. Bundy, 1877, is due the credit of introducing the bark of *Rhamnus Purshiana* (cascara sagrada) to the medical profession. In 1877 he shipped a quantity of the bark to Parke, Davis and Company, of Detroit, Mich., who in 1878 made the first pharmaceutical preparation (the fluidextract). To Parke, Davis and Company is therefore due the credit of bringing a preparation of this drug to the attention of physicians and pharmacists. Parke, Davis and Company were for a number of years the sole manufacturers of

preparations of this drug. ("Proc. of the Amer. Pharm. Assoc.," vol. 44, 1896, p. 198; *Practical Druggist*, August, 1910, p. 48; Bulletin of the Lloyd Library, No. 18, 1911, pp. 68, 69.)

Parke, Davis and Company state in one of their publications that they brought cascara sagrada to the notice of the British Medical Association at Cork in 1879.

Dr. C. H. Adair, of Colusa, Cal., a partner of Dr. Bundy, sent, in 1878, specimens of the bark and botanical specimens of the tree yielding it to J. U. Lloyd, of Cincinnati, Ohio. These, on identification by Curtis G. Lloyd, proved to be *Rhamnus Purshiana*, thus establishing the drug's botanical position. ("Proc. of the Amer. Pharm. Assoc.," vol. 44, 1896, p. 198; Bulletin of the Lloyd Library, No. 18, 1911, p. 70.)

In 1880 George W. Kennedy first published a formula for an elixir of *Rhamnus Purshiana*. ("Proc. of the Amer. Pharm. Assoc.," vol. 28, 1880, p. 431.)

Prof. W. T. Wenzell, in 1883, published a formula for an elixir of cascara sagrada, using potassium carbonate to remove the bitter principle. ("Proc. of the Cal. Pharm. Soc.," 1883; AMER. JOUR. OF PHARM., May, 1883, p. 252; "Proc. of the Amer. Pharm. Assoc.," vol. 31, 1883, p. 82.)

Mr. James G. Munson, a druggist of San José, Cal., in a letter to the writers under date of January 24, 1914, claims to have been the first to discover how to make tasteless fluidextract of cascara sagrada by the magnesium oxide process. This was in the fall of 1886, while he was in the employ of Prof. W. M. Searby, of San Francisco, Cal. Mr. Munson, however, did not publish a formula for the preparation, and the method remained a trade secret. (*The Pacific Druggist*, June 15, 1890, p. 27.)

Dr. Fred A. Grazer, of Sacramento County Hospital, Sacramento, Cal., in a letter to the writers under date of November 21, 1913, states that Prof. W. M. Searby, of San Francisco, Cal., was the first to introduce a preparation of bitterless fluidextract of cascara sagrada which was offered for sale by retail druggists. The method of manufacture was a secret process, no formula being published. Dr. Grazer published the first formula for the preparation of a bitterless fluidextract of cascara sagrada, using calcined magnesia to remove the bitter principle. (*Pharmaceutische Rundschau*, Jan., 1888, p. 9; "Proc. of the Amer. Pharm. Assoc.," vol. 36, 1888, p. 253.)

Parke, Davis and Company, of Detroit, Mich., in their pamphlet

on "Cascara Sagrada and its Preparation," state that they have a formula (No. 536), under date of 1887, for the manufacture of aromatic (tasteless) fluid cascara sagrada.

R. Wright published, in 1888, a formula for a bitterless fluid-extract of cascara sagrada, using calcined magnesia to remove the bitter principle. ("Yearbook of Pharmacy," 1888, pp. 395, 396; "Proc. of the Amer. Pharm. Assoc.," vol. 37, 1889, p. 381.)

Professor John M. Maisch ("Proc. of the Amer. Pharm. Assoc.," vol. 38, 1890, p. 394) calls attention to the fact that H. R. Slack, Jr.,



FIG. 6.—Sun-drying Cascara bark on platform of abandoned saw-mill.

recently recommended *Rhamnus Purshiana* for pharmacopœial recognition before the Georgia Pharmaceutical Association.

The bark first became official in the United States Pharmacopœia in the 1890 edition.

HISTORY OF THE CHEMISTRY OF RHAMNUS PURSHIANA.—The first chemical examination of the bark was made by Dr. A. B. Prescott, who isolated a brown resin of strong, bitter taste, colored vivid purple-red by potassium hydroxide solution; a red resin, nearly tasteless, colored rich brown by potassium hydroxide solution; a yellow resin or a neutral body, tasteless, colored bright red-brown by sulphuric acid, not colored by potassium hydroxide solution. He also

isolated a crystallizable body in white double pyramids, and some other form of dimetric system. Tannic acid, oxalic acid, malic acid, a fixed oil, a volatile oil, wax, and starch were also found. (AMER. JOUR. OF PHARM., vol. 51, 1879, p. 165.)

Limousin (*Jour. de Pharm. et de Chim.* (5), vol. 6, 1885, p. 80; "Proc. of the Amer. Pharm. Assoc.," vol. 33, 1885, p. 188) considered that the resins obtained by Prescott were derived from chrysophanic acid, which he believed to be present in notable quantities. According to H. A. D. Jowett ("Proc. of the Amer. Pharm. Assoc.," vol. 52, 1904, p. 288) these deductions are incorrect. He believes that emodin, which he claims is present, will give the characteristic reactions thought to be due to chrysophanic acid.



FIG. 7.—A means of moving dried Cascara bark to bark cutter.

W. T. Wenzell (*Pharm. Rundsch.*, vol. 4, 1886, p. 79) isolated from the bark a small quantity of an orange-red, crystalline substance, melting at  $226^{\circ}$ – $230^{\circ}$  C., and having the properties of a glucoside. Later investigators have shown that it was impure emodin.

H. F. Meier and J. L. Webber (AMER. JOUR. OF PHARM., vol. 60, 1888, p. 87) found, as a result of their investigation, a glucoside, a ferment, glucose, and traces of ammonia.

Paul Schwabe (*Archiv. der Pharm.*, vol. 226, 1888, p. 569) examined *Rhamnus Purshiana* and found emodin, identical with that of *Rhamnus frangula*, to exist as such in the bark, and identified it by means of its acetyl and di-bromo compounds, all of which were

analyzed. He considered that Wenzell's crystals, previously referred to, were merely impure emodin, and could obtain no evidence of the existence of a glucoside, nor could he isolate any other crystalline substance.

Dr. Eccles reports in the *Druggists' Circular* of March, 1888, p. 54, the discovery of the presence of an alkaloid which he states he has separated from the fluidextract and precipitated by Mayer's reagent.

A. C. Zeig ("Proc. of the Amer. Pharm. Assoc.," vol. 37, 1889, p. 261) further examined the resins previously described by Prescott, but was unable to isolate any definite principle.

Le Prince (*Compt. rend.*, vol. 115, 1892, p. 286) claims to have obtained the active principle of cascara bark in a crystalline form and named it cascarine. Le Prince suggested that cascarine might be identical with rhamnetin.

A most curious confusion has arisen in chemical literature with respect to this substance. Beilstein ("Handbuch," 3rd edition, vol. 3, p. 627), under cascarine, states that it is identical with rhamnetin, but Phipson (*Compt. rend.*, vol. 115, 1892, 474) considers that it was identical with xantho-rhamnin, and Van Rijn ("Die Glykoside," 1900 edition, p. 299), without comment, accepts this latter statement, and under xantho-rhamnin gives the details of Le Prince's preparation of cascarine from cascara.

The properties of cascarine, as given by Le Prince, prove that it could not be identical with either rhamnetin or xantho-rhamnin. Le Prince presents no evidence of the purity of cascarine; it agrees, however, in properties, with the exception of the melting-point, with emodin.

E. Cabanes states that the active principles of cascara bark are located in the layers of bast immediately adjoining the cambium, and in the medullary rays traversing these layers. (*Pharm. Jour.*, May 2, 1896, p. 343; *Rep. de Pharm.* (3), vol. 7, p. 97; "Proc. of the Amer. Pharm. Assoc.," vol. 44, 1896, p. 638.)

A. R. L. Dohme and H. Englehardt ("Proc. of the Amer. Pharm. Assoc.," vol. 45, 1897, p. 193) examined *Rhamnus Purshiana* and claimed to have isolated the active principle of the drug, which they named Purshianin. This was stated to be a glucoside, yielding, on hydrolysis, emodin and a sugar which was not identified. They consider the fat to be a mixture of dodecyl palmitate and stearate. They also attempted to obtain the bitter principle in a crystalline form, but were unsuccessful.

H. A. D. Jowett ("Proc. of the Amer. Pharm. Assoc.," vol. 52, 1904, p. 295) summarizes the results of previous investigators as follows:

1. The only definite principle isolated from cascara bark, the identity of which can be considered to be absolutely established, is emodin.

2. The statement of the existence in the bark of chrysophanic acid, chrysarobin, or glucosides yielding on hydrolysis emodin, chrysophanic acid, or rhamnetin, is not supported by satisfactory experimental evidence.



FIG. 8.—Cutting and sacking dried Cascara bark.

3. Wenzell's "crystals," Le Prince's "Cascarine," and Dohme and Engelhardt's "Purshianin" would appear, from the descriptions given by the respective authors, to be merely impure emodin.

4. No indication can be given of the identity of the crystals described by Prescott.

5. It has been stated by Dohme and Engelhardt that the fat of cascara consists of dodecyl palmitate and stearate.

Mr. Jowett ("Proc. Amer. Pharm. Assoc.," vol. 52, 1904, pp. 288-295), in his investigations, confirmed the presence of emodin in cascara, and also isolated a substance which he called isoemodin. He also found glucose and syringic acid. No evidence was obtained of the existence of chrysophanic acid, chrysarobin, or glucosides yielding on hydrolysis emodin, chrysophanic acid, or rhamnetin.



No substance corresponding to either cascarine or purshianin was found. The fat was found to consist of rhamnol arachidate and free arachidic acid. A hydrolytic enzyme was isolated. The bitter and the active principles of the bark were not isolated.

CHEMICAL CONSTITUENTS.—The chemical constituents of *Rhamnus Purshiana* are being studied by the writers, and the results of the investigation will appear in a later issue of this journal.

ACKNOWLEDGMENTS.—The authors wish to express appreciation to Dr. John Uri Lloyd, of the Lloyd Library, Cincinnati, Ohio, and Dr. John M. Francis, of Parke, Davis and Company, Detroit, Mich., for historical facts; to Prof. Hugo Winkenwerder, dean of the University of Washington College of Forestry, for facts concerning *Rhamnus Purshiana* in the State of Washington; to Dr. Fred A. Grazer, of Sacramento, Cal., and Mr. James G. Munson, of San José, Cal., for facts relating to the first bitterless preparations of the bark; to Mr. Floyd E. Ryus, of Ketchikan, Alaska, for information concerning the growth of the tree in Alaska; to Mr. Carl L. Kurtz, of Notus, Idaho, for information concerning its growth and range in Idaho; to Mr. H. E. Holmes, of Stewart & Holmes Drug Company, Seattle, Wash.; Mr. Geo. D. Prigmore, a druggist, of Chehalis, Wash., and Mr. Charles A. Richey, of Seattle, Wash., for data concerning the growth of the tree and collection of the bark in Washington.

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## THE INSECTICIDAL VALUE OF FLUIDEXTRACT OF LARKSPUR SEED.\*

By J. B. WILLIAMS.

An examination of several samples of fluidextract of larkspur seed on the market at the present time showed a very marked difference in their physical, chemical, and insecticidal properties. The samples examined varied in color from a dark brown to a very light yellow; the alcoholic content from 40 per cent. to 80 per cent., the fixed oil content from less than 0.2 per cent. to nearly 20 per cent., the alkaloidal strength from 0.43 per cent. to over 1 per cent., while the insecticidal value varied 500 per cent. (1 to 5).

With the object in view of determining if possible the constituent of larkspur seed to which it owes its insecticidal properties, and the best means of extracting the same, a number of fluidextracts were prepared, using various menstrua. The resulting fluidextracts were assayed for alkaloidal content and also for fixed oil, and their insecticidal value was determined by tests on living insects (bedbugs). The seed used was that of *Delphinium ajacis*, L., and was ground to a No. 30 powder. The methods of extraction were as follows:

No. 1.—Extracted by percolation with 95 per cent. alcohol, the strong percolate reserved and extraction continued until the drug was practically exhausted; the weak percolate evaporated to a soft extract and dissolved in the reserved portion, and sufficient 95 per cent. alcohol added to make 1 c.c. for each gramme of drug used. Upon standing this fluid separated into two well-defined layers, the upper oily layer equalling about 45 per cent. and the lower layer about 55 per cent. of the whole. These were separated and each made up to the original volume with 95 per cent. alcohol and, for purposes of identification, marked 1-A for the upper and 1-B for the lower layer.

No. 2.—Extracted by percolation in usual manner with dilute alcohol.

No. 3.—Extracted with 30 per cent. alcohol.

No. 4.—Extracted with petroleum benzine, the benzine removed

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\* Presented at the meeting of the American Chemical Society at Rochester, N. Y., September, 1913.

by evaporation on the water-bath and the residue dissolved in 95 per cent. alcohol.

No. 5.—Extracted with petroleum benzine, the benzine solution shaken out with dilute acid to remove the greater part of the alkaloid, then evaporated and the residue dissolved in 95 per cent. alcohol.

No. 6.—Extracted with 10 per cent acetic acid, the acid removed by distillation and the residue dissolved in dilute alcohol.

No. 7.—The drug residue from No. 6 extracted with 95 per cent alcohol.

No. 8.—Extracted with 95 per cent. alcohol until a yield of 1 c.c. for each gramme of drug used was obtained. This gave a perfectly clear fluid, showing no signs of separating after standing several weeks.

No. 9.—The extraction of drug residue of No. 8 continued until a further yield of 1 c.c. for each gramme of drug used was obtained.

No. 10.—The alkaloidal residues of several assays dissolved in sufficient 95 per cent. alcohol to make a 1 per cent. solution.

These fluidextracts varied in color from a dark brown (No. 6) to a very light yellow, and after standing several weeks, with the exception of Nos. 2, 3, and 6, which show some sediment, are in good condition.

The alkaloid and fixed oil contents are as follows:

	Color	Alkaloid	Oil
1 {	1-A. .... Pale yellow	0.26	21.34
	1-B. .... Yellow	0.81	7.08
2.....	Dark brown	1.42	0.19
3.....	Dark brown	1.26	0.12
4.....	Pale yellow	0.17	30.37
5.....	Pale yellow	0.05	30.54
6.....	Very dark brown	1.24	0.14
7.....	Yellow	0.06	23.67
8.....	Yellow	0.60	24.76
9.....	Pale yellow	0.11	3.60
10.....	Reddish yellow	1.0 (not assayed)	

The drug itself assayed 1.78 per cent. alkaloids and 36.1 per cent. oil.

The insecticidal values of the fluids were determined by Mr. H. C. Hamilton by the method of Houghton & Hamilton.\* The results were as follows:

\* Eleventh Report of the Michigan Academy of Science, 1909.

	Effective dilution	Coefficient.
1 { 1-A.....	1-120	6.0
1 { 1-B.....	1-50	2.5
2.....	1-18	0.9
3.....	1-12	0.6
4.....	1-120	6.0
5.....	1-150	7.5
6.....	1-18	0.9
7.....	1-120	6.0
8.....	1-100	5.0
9.....	1-15	0.75
10.....	1-12	0.6
11 standard...	1-20	1.0

From the above results it would appear that it is the oil and not the alkaloid to which larkspur seed owes its insecticidal properties, and, since the fluid is seldom used internally but almost exclusively as an insecticide, it would seem that the menstruum that will extract the largest amount of oil is the proper one to use. It should be noted, however, that the alkaloid has a slight insecticidal value, as the sample containing 1 per cent. of alkaloid and no oil was one-tenth as active as the samples containing a high content of oil.

ANALYTICAL AND EXPERIMENTAL DEPARTMENT,  
PARKE, DAVIS & CO., Detroit, Mich.

## PROGRESS IN PHARMACY.

A QUARTERLY REVIEW OF SOME OF THE MORE INTERESTING LITERATURE RELATING TO PHARMACY AND MATERIA MEDICA.

By M. L. WILBERT, Washington, D. C.

The European war has precipitated a condition unprecedented and unparalleled in the history of the drug trade of this country, and has demonstrated as no other line of argument possibly could that we in America are still largely dependent on European countries for our supplies of drugs and chemicals. More than 50 per cent. of the drugs and chemicals used in pharmacy and allied industries has been subjected to marked advances in price. The available stocks of many articles of a staple nature appear to have been at a rather low level, and some of the chemicals of German origin are already practically exhausted.

It will no doubt be months before the drug market can adjust

itself to the suddenly changed conditions, and the ultimate solution of the problems that are now presented will be eagerly awaited by all. The influence that the changed conditions will have on American Pharmacy should be a beneficial one, as the present scarcity of articles that could be made will no doubt stimulate the growth of chemical industries in this country.

Considerable concern has been expressed as to the whereabouts of the German-American apothecaries and their friends who in their trip through Europe reached Bremen on July 13. They were the guests of the Berlin apothecaries on July 15, 16 and 17. (*Apoth.-Ztg.*, 1914, vol. 29, pp. 644-645, 657-658.) An elaborate program had been prepared for their entertainment, one day being spent at the pharmaceutical institute of the University of Berlin at Dahlen. The apothecaries of Vienna, Munich, and several of the other large cities in Germany, Austria, Switzerland, and France had also prepared elaborate programs for entertaining the American pharmacists, but their itinerary has no doubt been interrupted by the general disturbance on the continent.

*Friederich Mohr*.—On June 21, 1914, there was unveiled in the city of Coblenz, Germany, a monument to one of the pioneers in pharmacy, Friederich Mohr, who despite the fact that he was the author of probably the original text-book on the practice of pharmacy is perhaps more widely known for his connection with the development of analytical chemistry than with that of galenical pharmacy. Pharmacists of an older generation will remember the book "Practical Pharmacy" by Mohr and Redwood, an American edition of which, edited by Wm. Procter, Jr., was in its day generally referred to as Mohr, Redwood and Procter's pharmacy. Friederich Mohr was born in the city of Coblenz in 1806, was a student at Bonn, Berlin, and Heidelberg, a voluminous writer, and is frequently referred to as the classic writer of pharmacy. His text-book of pharmaceutical technic was first published in 1847, his text-book on titration methods in 1855, and a commentary on the first edition of the German Pharmacopœia in 1874. Most of his life was spent in the pharmacy left him by his father and it was not until he reached his sixtieth year that he was called as a professor to Bonn, where he died in 1879.—*Apoth.-Ztg.*, 1914, vol. 29, pp. 547-550.

Before this copy of the JOURNAL reaches its readers the meetings of the National Association of Retail Druggists and the American Pharmaceutical Association will have become history. From present

indications both of these meetings will be interesting, profitable and well attended.

*The American Chemical Society's* summer or fall meeting, which was to have been held in the city of Montreal, Canada, September 15th to 18th, has been indefinitely postponed because of the European war and the present outlook is that the next meeting of the American Chemical Society will be held in New Orleans, April 1st to 3d, 1915.

*U. S. P. Revision.*—The fourth and fifth instalments of abstracts of proposed changes with new standards and descriptions for the United States Pharmacopœia, ninth revision, have been published. The first includes proposed proximate assays of crude drugs and galenical preparations and the latter embraces most of the biological products and volatile oils. The material so far published should prove a fruitful source for discussion at the Detroit meeting of the American Pharmaceutical Association.

*Official Assay Processes.*—Dichgans, H., in concluding a comparative examination of pharmacopœial methods for the assay of potent drugs and medicinal preparations, states that his results indicate that the directions for alkaloidal assay included in many of the pharmacopœias are not at all suited to the purpose. The results obtained are in many instances variable, while in others the methods are so complicated that they are unsuited for general practice. The different methods when applied to the same material give widely variable results, indicating that uniformity in the content of potent drugs can be secured only when the method of assay adopted is uniform.

*Total Extractive as a Factor in Fluid Extract Manufacture.* (Maines and Gardner.)—The determination of total extractive is an important factor in the manufacture of fluid extracts, especially those of the known alkaloidal drugs. A table of the total extractive determinations is given which represents estimations covering many years of work, and the products of several of the large manufactures.—*J. Am. Pharm. Assoc.*, 1914, vol. 3, pp. 997-1000.

*Useful Drugs.* (Report of the Board of Trustees.)—The work of the committee on a selected list of drugs has resulted in the publication of the book called "Useful Drugs." This has already been adopted as a text-book by a number of our best schools; its adoption has been considered by the State licensing boards, one already having adopted it, and there is every indication that this enterprise will have a most beneficial effect.—*J. Am. M. Assoc.*, 1914, vol. 63, p. 75.

*Prescriptions.* (Taylor, George B.)—A report on carelessness in the filling of simple prescriptions in the State of Louisiana. In December, 1913, a prescription calling for 2 gm. of boric acid and 2 ounces of distilled water was filled by 68 New Orleans druggists. Of these, 22, or 32.3 per cent., were correct both as to distilled water and to weight (some allowance is given in weight); 17, or 25 per cent., were correct as to weight but not as to the use of distilled water; 14, or 20.6 per cent., were correct as to distilled water but incorrect in weight; and 15, or 22.1 per cent., were incorrect both as to use of distilled water and as to weight.—*Rep. Louisiana Bd. H.*, 1912, 1913, pp. 176-187.

*Weights and Measures.*—In an address before the National Conference on Weight and Measures of Washington, D. C., Mr. F. P. Downing, chief inspector of weights and measures for the State of Wisconsin, referred to alleged inaccuracies in the delicate weighing apparatus in drug stores, jewelry stores, and the like. Coin weights used on such scales were stated by him to be often 10 to 30 per cent. light. In a recent inspection of drug stores in Milwaukee 22.1 per cent. of the dispensing scales and 43.6 per cent. of the dispensing weights in use were found in error.—*Pharm. J.*, 1914, vol. 92, p. 905.

*Food and Drugs Law.*—An important interpretation of the pure food and drugs act was handed down on June 13, by the United States Circuit Court of Appeals at Cincinnati in the case of the United States *vs.* Forty Barrels and Twenty Kegs of coca cola, which reads in part as follows: The general purpose and intent must be deemed to be the prevention of fraud and deception, so that the purchaser can get the thing he has a right to suppose he is getting, rather than the protection of the public health to the extent of preventing the purchaser from deliberately and intentionally buying a particular food which is what it purports to be, even though a jury might think it "deleterious."—*Druggists' Circular*, 1914, vol. 58, p. 487.

*The Patent Medicine Business.* (News Note.)—Dr. S. S. Goldwater, commissioner of health of New York City, has announced that a systematic investigation of the patent medicine business would be begun at once. It is proposed to insist that the manufacturer of a patent medicine name the ingredients in the mixture and it is believed that public opinion is sufficiently enlightened to support this movement.—*J. Am. M. Assoc.*, 1914, vol. 63, p. 411. See also *Druggists' Circular*, 1914, vol. 58, p. 481.

*Patent Medicines.* (Anon.)—Our Parliamentary correspondent learns that a further prolonged sitting of the Select Committee on Patent and Proprietary Medicines was held on Tuesday at the House of Commons. Sir Henry Norman, the Chairman, again presided. Altogether, the meeting lasted for some hours, and, as the result, about one-half of the draft report has now been disposed of.—*Chem. and Drug.*, 1914, vol. 85, p. 223.

*Consumption Cure.* (Editorial.)—After a hearing extending over seven days, the libel action against the British Medical Association brought by Mr. C. H. Stevens, the proprietor of "Stevens' Consumption Cure," has terminated in a verdict for the defendants. The jury, after an absence of about 10 minutes, found the matter complained of was of the nature of fair comment and judgment was accordingly given in favor of the British Medical Association.—*Pharm. J.*, 1914, vol. 93, p. 191.

*Proprietary Remedies.* (Editorial.)—The drug fund of the London Insurance Committee is threatened by the over-prescribing of proprietaries and the drugs and appliances sub-committee of the Insurance Committee has issued a list of articles as not being "proper and sufficient drugs and medicines and prescribed appliances required to be provided for insured persons," under the National Insurance Act.—*Chem. and Drug.*, 1914, vol. 85, p. 221.

*National Insurance Pharmacopœia.*—"Karshish" suggests the adoption of a national insurance pharmacopœia to avoid unnecessary deficiencies in the drug fund.—*Pharm. J.*, 1914, vol. 93, p. 11.

*British Pharmacopœia.* (London Letter.)—The work of preparing a new edition of the British Pharmacopœia has now been completed. One of the chief features will be that limits of impurity in drugs and medicinal chemicals—especially dangerous impurity—will be carefully defined. Another feature of the book is an extension of chemical standardization to drugs not at present standardized, but there is no recognition of physiologic standardization. The international unification of the quality of preparations of potent drugs, which has received the endorsement of various nations, has due recognition in the forthcoming book.—*J. Am. M. Assoc.*, 1914, vol. 62, p. 2039.

*British Pharmacopœia.* (Editorial.)—At its meeting on July 13 the Executive Committee of the General Medical Council formally adopted the completed draft of the British Pharmacopœia, 1914, as submitted by the Pharmacopœia Committee. It was resolved that



copies in advance of publication should be made accessible to the public for inspection at the offices of the Council in London, Edinburgh, and Dublin on Monday, August 10. The official publication of the Pharmacopœia will be made in the *London Gazette* on Friday, October 9, on which day copies will be on sale at the publishers.—*Pharm. J.*, 1914, vol. 93, p. 78.

*British Pharmaceutical Conference.*—The 51st annual meeting of the British Pharmaceutical Conference was held at Chester, July 20 to 25, 1914, presided over by Edward H. Farr, who chose for the subject of his presidential address a discussion of recent work on plant products. The proceedings are reported at length in the British pharmaceutical journals for July 25, 1914, and the papers presented are published in the journals of the same date. The total number of papers presented was 28, of which 25 were read in the ordinary section and 3 in the practice section. The nature of these communications was well up to the average and should prove to be of interest to all who are in any way engaged in the practical side of their profession.—*Pharm. J.*, 1914, vol. 93, pp. 117-139; also *Chem. and Drug.*, 1914, vol. 85, pp. 161-195.

The papers read in the ordinary section of the British Pharmaceutical Conference included the following:

*Estimation of Strychnine in the Presence of Brucine.* (Ditt, D. B.)—A modification of Gordon's process is recommended, the experimental data recorded showing that the use of 1 c.c. of concentrated nitric acid for each 0.25 Gm. of brucine in the proportion of 1 to 10 volumes of acid solution, made for a period of 20 minutes at ordinary temperature, is quite sufficient to destroy all the brucine.—*Pharm. J.*, 1914, vol. 93, p. 120.

*The Purity of Pepsin Bacteriologically Considered.* (Quant Ernest.)—A report on 11 samples of pepsin from various sources, only two of which were free from micro-organisms. The author suggests that the product may be improved by the presence of free acid and the use of chloroform.—*Pharm. J.*, 1914, vol. 93, pp. 120, 121.

*The Adulteration of Belladonna Leaves.* (Allen and Deane.)—The leaves of *Phytolacca decandra*, *Scopola carniolica*, and *Ailanthus glandulosa* were found admixed with commercial belladonna from Continental sources to the extent of from 20 to 80 per cent. The authors review the literature and present a number of illustrations showing the macroscopic and microscopic features of the

several substitutes compared with the distinguishing features of the genuine drug.—*Pharm. J.*, 1914, vol. 93, pp. 121-123.

*The Rate of Dialysis of Alkaloids in Aqueous Solution and in the Form of Galenicals.* (Finnemore, H.)—From experiments reported the author concludes that strychnine in aqueous solution diffuses more rapidly than in the form of the liquid extract of nux vomica, and this fact may have some bearing on the therapeutic effect of the two.—*Pharm. J.*, 1914, vol. 93, pp. 123, 124.

*The Incompatibility of Strychnine and Nux Vomica with Alkalies, Iodides, and Bromides.* (Finnemore and Williamson.)—The most striking feature of the experiments now recorded is the difference in the behavior towards alkalies of strychnine in the form of the solution and that existing in its natural state in admixture or combination with the other ingredients of nux vomica seeds. It appears that, whereas strychnine and alkalies or iodides may become dangerous under varied and indeterminate conditions, when the drug is given in the form of the tincture or the liquid extract no precipitation occurs and no danger need be apprehended, provided the concentration is not greater than that found under normal conditions of prescribing and dosage.

*The Analytical Characters of Benzoin.* (Cocking and Kettle.)—The alcohol soluble matter in benzoin is not readily determined directly, owing to the volatility of the balsamic constituents, and the easiest way is to obtain it by exhausting the drug by alcohol. A modified method for the determination of the aromatic acid is suggested, and a table showing the composition of a number of the commercial samples of the drug is included with the paper.—*Pharm. J.*, 1914, vol. 93, pp. 125, 126.

*The Mineral Constituents of Certain Tinctures and Drugs.* (Lewis, S. Judd.)—The molecular structure of chlorophyll is very closely related to hæmatin, the red coloring matter of the blood. The former, under the influence of light, brings about the absorption of carbon dioxide by plants and the elimination of oxygen, and has magnesium as an essential element, hence magnesium is to be anticipated in all mineral matter which has passed through the vegetable cell. The presence of iron is also necessary for the formation of chlorophyll, although it does not enter into the constituents of the pigment. Potassium and calcium are also constantly present, and the occurrence of other metals is frequently more or less accidental. Sodium is widely distributed, while lithium,

aluminum and manganese are rarely encountered. Copper is not rare. Among the non-metals, sulphur and phosphorus are nearly always present in the ashes of plants.—*Pharm. J.*, 1914, vol. 93, pp. 126-128.

*The Stability of Cinnamic Aldehyde.* (Phillips, H. Adie.)—It has been contended that in the distillation of the oil from chips there was a likelihood that some of the cinnamic aldehyde was oxidized to cinnamic acid. The experiments reported seem to prove that under the usual conditions prevailing under steam distillation cinnamic aldehyde, both pure and as a constituent of cinnamon oil, is not appreciably oxidized.—*Pharm. J.*, 1914, vol. 93, pp. 129, 130.

*The Composition of Tinctura Iodi Decolorata.* (Pratt, Walter R.)—The finished tincture made according to the directions of the British Pharmaceutical Codex is an alcoholic solution of ammonium iodide, with excess of ammonia containing about 0.1 per cent. iodoform and in some cases ammonium iodate, hydroxylamine, and acetaldehyde.—*Pharm. J.*, 1914, vol. 93, pp. 130, 131.

*The Determination of Iron in the Presence of Phosphoric Acid.* (Corfield and Pratt.)—The gravimetric determination of ferric iron in the presence of even small quantities of phosphates gave results which are much too high and are variable among themselves. Both the idiometric and reduction by stannous chloride volumetric methods give results which are very accurate and can be equally well used in the presence of phosphoric acid. The former method gives results which tend to be somewhat high.—*Pharm. J.*, 1914, vol. 93, pp. 131-133.

*An Improved Method for the Administration of Extractum Filicis Maris Liquidum.* (Crossley, Holland F. W.)—Oleo-resin of aspidium can best be exhibited in the form of a jelly made with gelatin and glycerin, sweetened with saccharin and flavored with oil of cinnamon. This form of preparation is said to be more palatable than emulsions or capsules, and the bulk is reasonable in relation to the dose.—*Pharm. J.*, 1914, vol. 93, p. 133.

*The place of Carbon Disulphide in Official Pharmacy and Suggestion for its Further Use.* (Alcock, F. H.)—The use of carbon disulphide is recommended as a solvent for fats and as a means for ascertaining the amount of constituents extractable from official liquid preparations, such as liquid extracts and tinctures. Some useful results have been obtained, a number of which are recorded.—*Pharm. J.*, 1914, vol. 93, pp. 133, 134.

*The Composition of the Glycerophosphates of Commerce.* (Um-

ney and Bennett.)—Calcium glycerophosphate is of variable composition and does not contain a definite proportion of water. Potassium glycerophosphate is not readily obtainable in a crystalline form, and the crystalline form of sodium glycerophosphate contains 5 molecules of water. Magnesium glycerophosphate is rendered more soluble by the presence of citric acid, and no definite formula for the hydrated salts can be given. Ferric glycerophosphate should contain approximately 15 per cent. of metallic iron and should be completely soluble in two parts of water.—*Pharm. J.*, 1914, vol. 93, pp. 134, 135.

*Commercial Standards for Dried Magnesium Sulphate, Sodium Sulphate, and Sodium Phosphate.* (Umney and Bennett.)—A reasonable standard for dried magnesium sulphate would be that it should be prepared by drying at 100° until it has lost about one-third of its weight, and that the product should contain not less than 23 per cent. and not more than 31 per cent. of water. It should be completely and readily soluble in water. Sodium sulphate should be practically anhydrous and should not contain more than 5 per cent. of water. For sodium phosphate 5 per cent. of water would be a reasonable limit.—*Pharm. J.*, 1914, vol. 93, pp. 135, 136.

*Liquor Opii Sedativus.* (Bennett and Cocking.)—Suggestions to improve the formula included in the British Pharmaceutical Codex. The opium should be exhausted by cold maceration in lime water, and the solution should be subsequently but slightly acidified by hydrochloric acid or sulphuric acid, after the addition of alcohol and wine.—*Pharm. J.*, 1914, vol. 93, pp. 136, 137.

*Some Uses of a Tincture Press.* (Pollard, E. W.)—An illustrated description of possible uses of a tincture press as a pill-piper or as a suppository machine.—*Pharm. J.*, 1914, vol. 93, pp. 137, 138.

*Anæsthetic Ether of Commerce.* (Finnemore, H.)—An examination of a number of samples of ether in actual use shows that, while some samples may have been rather inferior, in the main they have reached a fair average of purity. The impurities found consist of acetone, water, alcohol, acetaldehyde, peroxides, and acids.—*Pharm. J.*, 1914, vol. 93, pp. 138, 139.

*Medical Museum.* (Anon.)—The Wellcome Historical Medical Museum in London was reopened on May 28, 1914, in a permanent home, 54 A, Wigmore Street, Cavendish Square, London, W. The museum is open daily from 10 A.M. to 6 P.M., Saturdays to 1 P.M. Members of the medical profession and related callings

are admitted on the presentation of their visiting cards.—*Südd. Apoth.-Ztg.*, 1914, vol. 54, p. 403.

*The Hague Opium Conference.*—The third conference of representatives of the Powers for the purpose of regulating the production and distribution of opium, morphine, and cocaine and their derivatives was held at The Hague, June 23 to 25, 1914. It was concluded to be possible to put the convention into force notwithstanding the fact that some Powers have as yet not signed the convention in compliance with Article 23.—*Oil, Paint and Drug Rep.*, 1914, vol. 86, July 20, p. 18.

*Opium Suppression.* (Editorial.)—The difficulty of inducing an Oriental nation to do without some narcotic, and the danger of opium smoking being superseded by the still worse habits of cocaine and morphine injection, have long been noted. In the course of a recent trial it was stated that during the past two months about 200 pounds of morphine had been seized by the customs officials at Shanghai.—*Pharm. J.*, 1914, vol. 93, p. 78.

*Opium Habit.*—In answer to an inquiry the Secretary of State for the Colonies admits that it is the fact that the consumption of fermented liquors, especially beer and stout, had considerably increased in the Malay States since 1909, and the working of the Excise Enactments is being carefully studied with a view to the proper control of this consumption.—*Pharm J.*, 1914, vol. 93, p. 50.

*The Harrison Anti-narcotic Bill* was finally agreed to by the Senate on the afternoon of Saturday, August 15, in a form that will undoubtedly make it acceptable to members of the House and to the President.

*Smoking Opium.*—In May last the Commissioner of Internal Revenue made a decision regarding aqueous extract of opium, in which it was stated that, while this product may have some medicinal uses, such uses may be covered by the use of powdered extract of opium; also it is stated that the aqueous extract of opium is used to a considerable extent by opium smokers and is suitable for that purpose. Under the decision, the manufacturers of this product are required to comply with the law as to smoking opium. Taking up this subject, the Treasury Department has issued a decision calling attention to the action of the Commissioner of Internal Revenue, and stating that this product is within the scope of the smoking opium law passed on January 17, 1914, which prohibits the importation of such opium, and the collectors of customs are required to

refuse delivery of aqueous extract of opium and to return the importation to the country whence it came.—*Druggists' Circular*, 1914, vol. 158, p. 487.

*Boylan Law.* (A News Note.)—After an unavoidable delay in printing them, due to the failure of the State Legislature to make an appropriation therefor, the Boylan law order blanks, which must now be used by all pharmacists, druggists, physicians, dentists, and veterinarians in New York State, when buying opium and chloral, their derivatives and preparations containing the same, are now being distributed.—*Oil, Paint and Drug Rep.*, 1914, vol. 86, July 6, p. 11.

*Death by Poisoning in Great Britain.*—The 75th annual report of the Registrar-General of Births, Deaths, and Marriages in England and Wales shows that the number of deaths due to poisons and poisonous substances in 1912 was neither materially larger nor smaller than the average for recent years. The number of deaths certified as due to accidental poisoning by scheduled poisons was 122, against 124 in 1911, and by non-scheduled substances 102, against 115 in 1911. The number of cases in which poisons were taken by suicides was 547 (347 scheduled and 200 non-scheduled); in the previous year scheduled poisons were used in 324 cases, and non-scheduled in 195.—*Phar. J.*, 1914, vol. 93, p. 3.

*Responsibility for Poisoning.* (Anon.)—The responsibility for a fatal and an additional serious case of poisoning by impure barium sulphate, used in the course of a Röntgen-ray examination at Prague, has finally been fixed by the upper court at Vienna. This court decided that the pharmacist in charge of the pharmacy was responsible and guilty of neglect because of his having failed to carefully examine the barium sulphate before allowing it to be dispensed or used. The assistants in the pharmacy and in the wholesale drug establishment from which the barium sulphate had been purchased were freed, despite the objection made by the State's Attorney.—*Südd. Apoth.-Ztg.*, 1914, vol. 54, p. 403.

*Studies on the Absorption of Drugs.* (Hatcher and Eggleston.)—A summary of observations on the absorption of drugs, with the conclusion that the ratio of absorption from the four common channels of administration differs for each drug. No rule can be formulated for the calculation of the appropriate dose by one mode of administration from the dose by any other mode of administration. Such

determination can be made only by experiment.—*J. Am. M. Assoc.*, 1914, vol. 63, pp. 469-473.

*Algocratine*.—Mannich and Leemhuis, from the pharmaceutical laboratory of the University of Göttingen, report an examination of a powder offered as an infallible remedy for migraine, neuralgia, grippe, influenza, and other diseases. The preparation was found to consist essentially of a mixture of 50 Gm. phenacetin, caffeine 10 Gm., and pyramidon 40 Gm. The claims made for the composition of the preparation were found to be quite untrue.—*Apoth.-Ztg.*, 1914, vol. 29, p. 553.

*Antimeningitis Serum*. (Auer, John.)—It is an established fact that the administration of antimeningitic serum by intraspinal injection has practically turned the former 70 per cent. mortality from epidemic meningitis into 70 per cent. recoveries. Accumulated experience, however, has apparently shown that the injection of the serum itself may have been the cause of death in a very small number of cases. S. P. Kramer holds that they were caused by trikresol which had been added as a preservative to the serum, a contention which has recently been supported by Hale on the basis of experimental work on dogs and cats.—*J. Am. M. Assoc.*, 1914, vol. 62, p. 1799.

*Transformation of Barbaloin into Beta-barbaloin*. (Léger, E.)—When barbaloin is kept for some time near its melting-point, it becomes converted into its amorphous isomer, beta-barbaloin, which accompanies barbaloin in Cape and Socotrine aloes. The action of acetic anhydride on barbaloin at 100° to 110° also brings about the same change.—(*Compt. rend.*, 1914, vol. 158, p. 1903.) *Pharm. J.*, 1914, vol. 93, p. 83.

*Bichloride Tablets*. (Vanderkleed and E'we.)—"Bichloride" antiseptic tablet with tartar emetic administered to a dog produced profuse vomiting in seven minutes. During this time, however, a sufficient amount of the bichloride had been absorbed to cause the death of the dog in 6½ hours. This experiment indicates that to be effective the emetic must act more promptly than it did in this instance, as the absorption of bichloride takes place apparently very rapidly.—*Druggists' Circular*, 1914, vol. 58, p. 465.

*Calcium Therapy of Tuberculosis*. (Kahn, M.)—In looking over the mass of literature relating to the use of calcium in tuberculosis one is left in doubt whether the use of lime in the treatment of tuberculosis is to be recommended. There is, however, no danger

in its use, and, according to the observations of a number of physicians, it is of marked benefit.—(*Med. Rec.*, 1914, vol. 85, No. 21.) *J. Am. M. Assoc.*, 1914, vol. 62, p. 1844.

*The Determination of Camphor in Tablets and Pills.* (Dowzard, Edwin.)—Camphor may be rapidly and completely removed from tablets and pills by distillation in a current of steam. The watery distillate contains both dissolved and undissolved camphor, which can be extracted with benzol. By determining the optical rotation of the benzol solution the amount of camphor present in the tablets or pills can be readily calculated.—*J. Ind. Eng. Chem.*, 1914, vol. 6, pp. 489-490.

*Cerolin* (not Creolin as printed in the June issue of this JOURNAL, p. 279) consists of the glycerides of fatty acids along with cholesterins, lecithin, and ethereal oil, all of which are found in yeast. It is prepared by extracting fresh purified beer yeast with alcohol and separating the dissolved fat from the alcoholic extract by suitable means. Cerolin is said to be useful in furunculosis, acne, sycosis, and similar affections of the skin. It is also said to be useful in habitual constipation, leucorrhœa, erosions of the vagina and cervix, and similar diseases.—*J. Am. M. Assoc.*, 1914, vol. 62, p. 931.

*Cymarín.*—Wiesel considers cymarín a valuable supplement to digitalis because of the rapidity of its action.—*Therap. Monatsh.*, 1914, vol. 28, p. 508.

*Eisenzucker.* (Anon.)—Eisenzucker, or saccharated ferric oxide, is official in several pharmacopœias, but not in the United States Pharmacopœia. It consists of a ferric hydroxide made soluble by the addition of sugar and a small amount of sodium hydroxide. It is said to be an efficient ferruginous preparation. The adult dose is 0.6 Gm., or 10 grains. This may be dissolved in equal parts of water and syrup.—*J. Am. M. Assoc.*, 1914, vol. 63, p. 421.

*Electrargol.* (Puckner, W. A.)—Electrargol is a colloidal solution of silver containing a small percentage of sodium arabate. It contains silver equivalent to 0.25 per cent. metallic silver (Ag). Electrargol is an odorless, tasteless liquid, appearing transparent and reddish-brown by transmitted light and opaque and gray by reflected light. The addition of potassium cyanide solution or of strong nitric acid yields a white turbidity on the addition of chlorides.—*J. Am. M. Assoc.*, 1914, vol. 62, p. 1808.

*Friedmann Remedy.*—A number of clinicians and bacteriologists are beginning to report their experiences with the Friedmann remedy.



From the available reports it would appear that this remedy should not be used under any conditions until such time as a sufficient guaranty can be offered that the contaminations and pathogenic organisms present have been eliminated.—*Therap. Monatsh.*, 1914, vol. 28, pp. 509-511. See also *J. Am. M. Assoc.*, 1914, vol. 63, p. 177 and p. 358.

*Galegine Sulphate*.—The new base recently discovered and isolated by Tanret from *Galega officinalis*, the common goat's rue, is toxic when administered by hypodermic or intravenous injection, both for cold-blooded and warm-blooded animals.—(*Compt. rend.*, 1914, vol. 159, No. 108.) *Pharm. J.*, 1914, vol. 93, p. 195.

*Gitalin*. (Rosenthaler, L.)—Report of experiments which tend to confirm the assertion made by Kiliani that gitalin is not a definite substance.—*Schweiz. Apoth.-Ztg.*, 1914, vol. 52, pp. 349, 350.

*Glyco-Heroin, Smith*. (Puckner, W. A.)—The report of the Council on Pharmacy and Chemistry of the American Medical Association on glyco-heroin, Smith, shows it to be a dangerous mixture, containing the habit-forming drug heroin. It is exploited in "patent medicine style," and therefore destined to be misused by the unsuspecting laity.—*J. Am. M. Assoc.*, 1914, vol. 62, p. 1826.

*Hydrastinine in Hemorrhages of the Lung*. (Röher.)—A review of the use of synthetic hydrastinine in case of pulmonary hemorrhage. The synthetic hydrastinine is said to be identical with the natural substance, and its toxicity is comparable. The results in the five cases reported were uniformly satisfactory.—*Therap. Monatsh.*, 1914, vol. 28, pp. 505, 506.

*Idomenin*.—A combination of iodine, bismuth, and albumin that is not soluble in dilute acid solutions and is therefore not decomposed in the stomach, but asserts its influence in the intestinal tract in the form of an alkaline iodide and bismuth albuminate.—*Therap. Monatsh.*, 1914, vol. 28, p. 512.

*Luminal*.—Heinsius suggests that luminal should have established for it an official maximum dose, and that so long as this does not exist simple cases of insomnia should be given from 0.05 Gm. to 0.1 Gm. and not exceeding 0.3 Gm. per dose, this dose to be repeated not more than three times per day, with an interruption of from one to two days after four or five days' treatment.—*Therap. Monatsh.*, 1914, vol. 28, p. 514.

*Unusual Case of Fatal Poisoning from the Administration of Male-Fern as a Vermifuge*. (Hall, Maurice C.)—Report of a necropsy on a man who had died from an overdose of the oleoresin of

male-fern administered in amounts in excess of the usual dose, administration of which was followed by castor oil.—*J. Am. M. Assoc.*, 1914, vol. 63, pp. 242, 243.

*The Use of Maté.* (Editorial.)—Attention has recently been drawn, by means of letters to the *Times*, to the use of leaves known as *Yerba maté*, the tea plant of South America. The consensus of opinion seems to be that an infusion of the leaves forms a beverage eminently suited to a hot, debilitating climate, its stimulating effect being no doubt due to the caffeine it contains.—*Pharm. J.*, 1914, vol. 92, p. 870.

*Relative Bactericidal Power of Mercuric Salts.* (Stassana and Gompel.)—Mercuric iodide is found to be far more active as a bactericide than mercuric chloride, mercuric cyanide, or mercuric benzoate. It is at least ten times more powerful than mercuric chloride, which is generally considered to be one of the most active of all antiseptics.—*Pharm. J.*, 1914, vol. 93, p. 147.

*The Abuse of Normal Salt Solution.* (Litchfield, Lawrence.)—The administration of any artificial serum as routine postoperative practice is questionable therapeutics. Too much water may fatally embarrass the heart. Too much salt may fatally embarrass the kidneys. When fluids cannot be taken by the mouth, thirst may be relieved by tap-water or by isotonic dextrose solution given by enteroclysis.—*J. Am. M. Assoc.*, 1914, vol. 63, pp. 307-310.

*New Technic for Salt Solutions.*—Faege, K., outlines a method for the production of sterile salt solution from hydrant water, which depends on the addition of hydrochloric acid to ordinary hydrant water to sterilize it; then add sodium hydroxide in the proper proportion to produce sodium chloride in the desired percentage.—(*Münch. med. Wchschr.*, vol. 41, June 106, No. 24.) *J. Am. M. Assoc.*, 1914, vol. 63, p. 284.

*Liquid Petrolatum.* (Puckner, W. A.)—A review of the requirements for liquid petrolatum made in the existing pharmacopœias, some discussion of the history and present uses of the preparation, and descriptions of heavy and light liquid petrolatum, with titles to facilitate the dispensing of the products desired by the physician.—*J. Am. M. Assoc.*, 1914, vol. 62, pp. 1740-1742. (See this Journal, p. 322.)

*The Sterilization of Liquid Paraffin.* (Maughan, D.)—From the experiments reported it would appear that the application of heat at a temperature of 100° for half an hour is the most practical method

of rendering liquid paraffin sterile.—*Pharm. J.*, 1914, vol. 93, pp. 81, 82.

*Paraffin Cancer.* (Davis, Benjamin Franklin.)—Report of a case of cancer in one of the employees in the paraffin department of a large oil refining company located near Chicago, with discussion of coal and paraffin products as causes of chronic irritation and cancer. From a comprehensive review of the literature the author concludes that it would seem fair to assume that the chronic-irritation cancer produced by coal and petroleum products is a chemical-irritation cancer, and that it is not impossible that the cancer following chronic irritation of other origin may be of an essentially similar nature.—*J. Am. M. Assoc.*, 1914, vol. 62, pp. 1716–1720.

*Influence of Diet on the Toxicity of Phosphorus.* (Opie and Alford).—The toxicity of phosphorus, which causes fatty degeneration of the liver, is greater in animals which have received a diet of meat than in those which have received diets consisting in large part of carbohydrates or of fat.—*J. Am. M. Assoc.*, 1914, vol. 63, p. 137.

*Detection of Picric Acid in Urine.*—Among the French troops in Algeria a new form of malingering, by stimulating the symptoms of jaundice by taking picric acid, is not uncommon. To detect this the following reliable test for the acid in the urine has been devised: Five mls of the urine of the suspected case is heated to boiling, with an equal volume of saturated sodium hydroxide solution. Then 1 mil of ammonium sulphide solution is carefully floated on the surface of the liquid. In presence of picric acid, a red ring due to picramic acid will be formed at the zone of contact.—(*Répertoire*, 1914, vol. 26, No. 193.) *Pharm J.*, 1914, vol. 93, p. 195.

*Pituitary Extract.* (Roth, George B.)—Report of an examination of some commercial preparations made from the posterior lobe of the pituitary body. The relative values of five preparations by the blood-pressure method varied from 1 to 15, and the relative value of six samples by the isolated uterus method from 1 to 7.5. The use of beta-iminazolyethylamin hydrochloride is suggested as a standard for use on the isolated uterus method which is the only one applicable to all preparations.—*J. Am. M. Assoc.*, 1914, vol. 63, pp. 476–479.

*Prophylactic Use of Quinine in Malaria.* (Carter, H. R.)—The use of quinine in small doses is an efficient method for preventing malarial fever. This method is especially adapted for use in a farming community where it is not practicable economically to get rid of

malarial mosquitoes or to properly screen against them.—*J. Am. M. Assoc.*, 1914, vol. 62, p. 2042.

*Quinine in the Treatment of Syphilis.* (Breitmenn, M. J.)—The observation that the administration of quinine for the treatment of malaria in patients infected with syphilis was invariably accompanied by marked improvement of secondary and tertiary manifestations of the latter disease led to further experimentation and the use of a mixture of quinine muriate 3, with antipyrin 2, dissolved in from 6 to 8 c.c. of warm water. This mixture, designated chinopyrin, is injected subcutaneously and has given promising results.—*Therap. Monatsh.*, 1914, vol. 28, pp. 504, 505.

*Results of Radium in Cancer.* (Janeway, H. H.)—A survey of reported results, with the suggestion that a more successful method of applying radium may yet be discovered and that the whole question may reduce itself to the even distribution of the proper dosage throughout all involved tissues. At the present time radium may only supplement but not replace the knife.—*J. Am. M. Assoc.*, 1914, vol. 62, pp. 1707-1709.

*Dangers from Radium Treatment of Cancer.* (Rovsing, T.)—Tragic experiences in a number of cases lead to the conclusion that radium promotes instead of checks cancer.—*Hospitalstid.*, 1914, vol. 62, N. 27.) *J. Am. M. Assoc.*, 1914, vol. 63, p. 520.

*Production of Metallic Uranium.* (Anon.)—The steady increase in the production of radium at S. Joachimsthal, Austria, has resulted in an overproduction of uranium salts, which up to the present time are used only as coloring for glass and porcelain and have, therefore, but a limited application. Attempts have recently been made to produce metallic uranium by an electrolytic method, and these efforts promise to be successful. Further experiments are being undertaken with a view to utilizing the resulting material in the production of amalgams, more particularly the utilization of metallic uranium in the improvement of steel.—*Pharm. Post.*, 1914, vol. 47, p. 557.

*Pharmacological Instability of Scopolamine in Ampoules.* (Langer, H.)—To determine the pharmacological activity of scopolamine solutions, recourse was had to its antidotal action on muscarine in the isolated frog's heart. This test is quantitative, and much more reliable than the production of mydriasis in the cat's eye. From tests with the muscarine method, it is found that scopolamine salts kept in ampoules soon deteriorate, losing their specific action. Solutions of scopolamine for therapeutic use, therefore, should be freshly pre-

pared, and the employment of those in sterilized ampoules avoided as far as possible.—*Pharm. J.*, 1914, vol. 93, p. 147.

*Recordin*.—Mannich and Leemhuis, from the pharmaceutical laboratory of the University of Göttingen, report the examination of a preparation marketed as a prophylactic for the ills of old age, including arteriosclerosis. The analysis showed the substance to consist largely of sodium chloride, with negligible quantities of phosphates, sulphates, carbonates, and tartrates of calcium, magnesium, and sodium. As diluents bolus and starch were used.—*Apoth.-Ztg.*, 1914, vol. 29, p. 628.

*Rhubarb*. (Rosenthaler, L.)—A review of some of the available literature relating to the drying of rhubarb, from which the author concludes that this drug is always dried spontaneously, either out of doors or suspended in houses. The absence of gelatinized starch in the root indicates that higher temperatures are never used.—*Schweiz. Apoth.-Ztg.*, 1914, vol. 52, pp. 405, 406.

*The Control of Saccharin and Analogous Substances*.—The sovereigns and heads of the Governments of Germany, Belgium, Greece, France, Italy, the Netherlands, Portugal, and Russia, desiring to regulate the use of saccharin and allied substances, have agreed on articles describing the substances referred to, and have undertaken to prohibit the use of saccharin and other allied products in all beverages and foodstuffs.—*Perf. and Ess. Oil Rec.*, 1914, vol. 5, pp. 288, 289.

*Scillitin, the Toxic Principle of Squill*.—Kopaczewski, W., says he has isolated the toxic principle of squill in the form of an amorphous glucoside,  $C_{17}H_{25}O_6$ , to which the name scillitin is given. It is a very light, non-hygroscopic, intensely bitter powder. It is soluble in the saturated alcohols of the fatty series; sparingly soluble in water, and insoluble in ordinary organic liquids. It melts at  $152^{\circ}$  to  $154^{\circ}$ .—*Pharm. J.*, 1914, vol. 92, p. 879.

*Sennatin*. (Lindbom, Oskar.)—The intramuscular injection of sennatin produces, in the majority of cases of constipation, copious stools, with subjective and sensible peristaltic movements of the intestine. As an occasional complication marked increase in temperature was noted.—*Therap. Monatsh.*, 1914, vol. 28, p. 509.

*The Tablet Industry, its Evolution and Present Status, the Composition of Tablets and Methods of Analysis*. (Kebler, L. F.)—Historical review, with a report on the examination of a number of samples showing considerable variation in the nature of the tablets examined.—*J. Am. Pharm. Assoc.*, 1914, vol. 3, pp. 820-848, 937-958, 1062-1099.

*Compressed Tablets.* (Rohm, R.)—For the production of compressed tablets that will readily disintegrate, the addition of from 10 to 20 per cent. of magnesium peroxide is suggested. Tablets with this addition, when moistened with water, will disintegrate almost immediately.—*Sudd. Apoth.-Ztg.*, 1914, vol. 54, p. 398.

*Urease.* (Puckner, W. A.)—Urease is a preparation of the urealytic enzyme obtained from the soy bean, *Soja hispida*. It decomposes urea into ammonia and carbon dioxide, and it may be employed in the determination of the amount of urea in the urine, blood, and other body fluids. Urease is now being marketed by several firms as a fine, white powder with little taste or odor. It is soluble in slightly alkaline water, and represents the urea-converting enzyme of soy bean in a condition of high potency. It is practically free of the water-soluble proteins which are precipitated by hydrochloric acid, and of proteins that are insoluble in water.—*J. Am. M. Assoc.*, 1914, vol. 63, p. 165.

*Urotropin.*—Simon reports six cases in which hæmaturia followed the administration of fairly large doses of urotropin. In rabbits hæmaturia could be produced only by the administration of very large doses: 8 Gm. per day.—*Therap. Monatsh.*, 1914, vol. 28, p. 544.

*Uteramin.*—Uteramin is a new name applied to paraoxyphenylethylamine, formerly sold under the name systogen.—*Therap. Monatsh.*, 1914, vol. 28, p. 511.

*Wassermann Reaction in Tuberculosis.* (Letulle and others.)—It was found that 19 per cent. of 346 tuberculosis inmates of the Boucicaut Hospital gave a positive response to the Wassermann test. Only ten of the total of 64 reacting were aware of their syphilitic taint or had signs of it. Fourteen of the patients, including eight under 36, had some aorta affection.—*Bull. Acad. Méd.*, 1914, vol. 8, No. 4.) *J. Am. M. Assoc.*, 1914, vol. 62, p. 1848.

#### NEWS ITEM.

THE NATIONAL ASSOCIATION OF RETAIL DRUGGISTS ended in Philadelphia on August 21 the largest convention of druggists ever held in this country. Fully 1500 delegates, representing 20,000 members of the association, were present. The following officers were elected: President, Samuel C. Henry; Vice Presidents, A. S. Ludwig, W. H. Humphreys and T. C. Coltman; Secretary, Thomas H. Potts; Treasurer, Grant W. Stevens; Executive Committee, James F. Finerman, Robert J. Frick and T. S. Armstrong.

# THE AMERICAN JOURNAL OF PHARMACY

OCTOBER, 1914

## THE EXAMINATION OF SOME DRUGS WITH SPECIAL REFERENCE TO THE ANHYDROUS ALCOHOL AND ETHER EXTRACTS AND ASH.\*

By J. R. RIPPETOE, Analysts N. SMITH, W. TAYLOR, and G. STODDART.

As announced in the first paper bearing the above title,<sup>1</sup> in the examination of a number of commercial samples of vegetable drugs, in addition to identifying the samples and making specified tests for added or accidental impurities, such as starch, etc., we have attempted to make some assays that would serve as a means for determining the relative value of the sample when compared with some other sample or standard.

These assays have consisted chiefly in determining anhydrous extracts, alcohol and water, ether, chloroform, or petroleum ether, as may be suggested by the nature of the drug.

Since the appearance of the first paper we have examined a number of drugs along the same lines. The results of this work are given in the list appended, which list not only includes many of the names appearing in the first paper but also many drugs not heretofore considered.

For some drugs the value of determining the amount of anhydrous matter that may be extracted with various solvents has been pretty well established, also the determination of ash. This has been recognized by the Ninth Revision Committee of the U. S. P., and it is indicated<sup>2</sup> that a large number of official drugs are to have anhydrous or volatile extract and ash standards.

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\* Second Paper.

<sup>1</sup> First paper, Rippetoe and R. Minor, this JOURNAL, October, 1912, pp. 433-445.

<sup>2</sup> *J. A. Ph. A.*, March, 1914, p. 359.

### TABULATION OF ASSAYS.

SAMPLE	Sample No.	Alcohol extract Per cent.	Water extract, Per cent.	Ether extract Per cent.		Ash Per cent.	Remarks.
				Vol.	N. Vol.		
Agaric White.....	12573	62.05	.....	.....	.....	2.5	Insoluble ash 85.47 per cent.
Aletris.....G	11284	15.83 (49)	.....	.....	.....	17.96	
Aletris.....G	12783	16.68 (49)	.....	.....	.....	13.40	
Aletris.....G	13075	19.82 (49)	.....	.....	.....	11.29	Crude fibre 23.10
Alspice.....P	11347	.....	.....	.....	.....	3.44	
Aloes.....P	10808	74.14	86.67	.....	6.11	2.68	
Aloes, Barb.....W	12557	97.20	81.00	.....	.....	2.10	Contained some flowers and leaves. Contained some leaves.
Aloes, Cape.....P	10899	76.59	82.16	.....	.....	1.20	
Aloes, Cape.....P	11139	90.49	62.74	.....	.....	4.03	
Aloes, Cape.....P	13250	92.50	67.50	.....	.....	1.50	
Aloes, Cape.....P	12517	84.20	63.70	.....	.....	4.70	
Aloes, Cape.....W	13373	88.52	61.16	.....	.....	0.81	
Aloes, Curacao.....P	11138	92.19	72.66	.....	.....	2.55	
Aloes, Curacao.....P	11843	92.03	73.75	.....	.....	2.85	
Aloes, Curacao.....P	12929	89.48	71.99	.....	.....	3.19	
Aloes, Curacao.....W	11016	84.60	52.71	.....	.....	5.08	
Aloes, Socotrine.....P	12890	84.09	52.01	.....	.....	5.34	
Aloes, Socotrine.....P	11149	83.62	52.85	.....	.....	4.05	
Aloes, Socotrine.....P	13185	84.00	52.85	.....	.....	6.50	
Althea Root.....P	11084	.....	21.22	.....	.....	7.08	
Althea Root, Cut.....P	11577	.....	28.60	.....	.....	6.93	
Arnica Flowers.....G	10897	20.81 (49)	.....	.....	.....	7.78	
Arnica Flowers.....G	12054	24.25 (49)	.....	.....	.....	6.80	
Arnica Root.....W	11037	18.72 (49)	.....	.....	.....	8.93	
Arnica Root.....W	10750	24.13 (49)	.....	.....	.....	12.92	
Arnica Root.....W	10751	26.37 (49)	.....	.....	.....	6.64	
Asclepias.....G	12506	25.30 (49)	.....	.....	.....	3.95	
Asclepias.....G	13005	19.19 (49)	.....	.....	.....	3.51	
Asclepias.....G	13324	27.80 (49)	.....	.....	.....	6.03	
Avena Sativa.....G	13092	7.22 (25)	13.03	.....	.....	2.65	
Berbers.....G	13282	8.15 (49)	.....	.....	.....	2.15	
Buchu Short.....W	11219	20.30 (73)	.....	.....	.....	3.91	
Buchu Short.....W	11220	20.33 (73)	.....	.....	.....	4.13	
Buchu Short.....W	11221	20.46 (73)	.....	.....	.....	3.80	
Buchu Short.....W	11794	22.53 (73)	.....	.....	.....	3.71	
Buchu Short.....W	11842	20.09 (73)	.....	.....	.....	4.15	



Buchu Short.....	W	12052	17.45	.....	1.80	5.70	4.35	6.33 of stems
Buchu Short.....	W	12053	16.90	.....	0.85	5.50	3.95	8.13 of stems
Buchu Short.....	W	12054	17.80	.....	0.85	6.45	3.70	8.90 of stems.
Buchu Short.....	W	12055	18.70	.....	0.75	5.05	4.60	15.18 of stems.
Buchu Long.....	W	11331	19.56 (73)	.....	1.61	3.97	5.00	15.41 per cent. of stems and other leaves.
Buchu Long.....	W	11691	19.87 (73)	.....	2.04	4.11	5.22	13.58 of stems.
Buchu Long.....	W	12096	24.90 (73)	.....	0.90	5.00	4.20	14.12 of stems.
Buckeye Bark.....	G	13391	9.1	11.3	0.20	4.2	4.1	
Calcutia.....	P	11079	25.94 (65)	.....	.....	.....	10.34	
Calumia Root.....	G	12044	13.05 (65)	.....	.....	.....	5.88	
Cannabis Americana.....	W	13357	20.6	.....	.....	17.65	8.20	46.75 per cent. of seed.
Cannabis Americana Seeds.....	W	13357	23.35	.....	.....	25.7	4.25	
Cannabis Americana Seedless.....	W	13357	13.30	.....	.....	0.80	11.60	
Cannabis Indica.....	W	10950	16.35	.....	.....	15.52	13.82	7.35 per cent. of seeds.
Cannabis Indica.....	W	11252	15.07	.....	1.81	13.57	13.95	4.16 per cent. of seeds.
Cannabis Indica.....	W	11993	14.35	.....	.....	.....	15.05	4.41 per cent. of seeds.
Cannabis Indica.....	W	11081	14.50	.....	.....	.....	14.70	5.76 per cent. of seeds.
Cannabis Indica.....	W	12083	12.30	.....	.....	.....	14.50	4.50 per cent. of seeds.
Cannabis Indica.....	W	12147	13.70	.....	.....	.....	13.80	5.30 per cent. of seeds.
Cannabis Indica.....	W	13337	13.05	.....	.....	12.40	13.20	9.40 per cent. of seeds.
Cannabis Indica.....	W	13547	14.80	.....	.....	.....	13.30	2.55 per cent. of seeds.
Cannabis Indica.....	W	13593	14.00	.....	.....	.....	4.88	3.88 per cent. of seeds.
Cantharides.....	P	11593	.....	.....	.....	20.60	7.01	
Cantharides.....	P	11702	.....	.....	.....	17.36	7.21	
Cantharides.....	P	13697	.....	.....	.....	12.35	5.05	
Capsicum.....	P	11349	17.02	.....	2.38	16.49	4.87	
Capsicum.....	P	11663	24.46	.....	.58	17.27	7.00	
Capsicum.....	P	12077	.....	.....	.70	16.55	6.25	
Capsicum.....	G	12596	19.50	.....	.6	17.88	6.94	
Caraway Seed.....	P	11058	20.88	.....	4.30	18.82	6.11	
Cardamom Seed.....	W	11166	4.16	.....	1.93	1.35	7.52	
Cardamom Seed Decort.....	W	11092	4.07	.....	1.0	1.81	4.55	
Cardamom Seed Decort.....	W	11122	6.02	.....	2.43	2.13	4.55	
Cardamom Seed Decort.....	W	11943	3.95	.....	1.75	2.25	5.75	
Cardamom Seed Decort.....	W	13186	3.20	.....	-35	2.10	5.85	
Cascara Sagrada.....	G	10532	24.55	26.97	.....	4.61	.....	1.8 per cent. of foreign matter
Cascara Sagrada.....	G	11888	25.00	27.36	.....	4.28	.....	
Cascara Sagrada.....	G	11888	22.20	28.05	.....	4.37	.....	
Celery Seed.....	P	11605	22.4	.....	1.46	22.25	12.66	
Celery Seed.....	P	11795	6.32	.....	1.28	11.18	22.07	
Celery Seed.....	P	12497	25.65	.....	2.10	26.30	17.85	
Chamomile, Flowers.....	W	11603	22.58	.....	2.06	7.02	5.56	
Belgian.....	W	1212	34.82 (49)	.....	.....	.....	5.30	
Chimaphila.....	G	12842	36.11 (49)	.....	.....	.....	5.88	
Chimaphila.....	G	12842	.....	.....	.....	.....	.....	

TABULATION OF ASSAYS—(Continued)

SAMPLE	Sample No.	Alcohol extract Per cent.	Water extract, Per cent.	Ether extract Per cent.		Ash Per cent.	Remarks.
				Vol.	N. Vol.		
Cimicifuga.....G	12046	12.20	.....	.....	.....	9.30	
Cimicifuga.....G	13420	6.43	.....	.....	.....	8.93	
Cinnamon, Ceylon...P	11863	14.33	.....	.....	.....	4.01	
Cloves.....G	11669	.....	.....	.....	.....	5.00	
Cloves.....P	12001	16.20	.....	.....	.....	6.85	
Colocynthis Pulp...P	11840	.....	.....	.....	.....	12.95	1.21 per cent. Petroleum ether
Colocynthis Pulp...P	11844	.....	.....	.....	.....	13.28	.50 per cent. Petroleum ether
Colocynthis Pulp...P	11947	.....	.....	.....	.....	14.15	1.42 per cent. Petroleum ether
Colocynthis Apple...G	12846	18.46 (49)	.....	.....	.....	4.73	8.24 per cent. Petroleum ether
Coltsfoot.....G	13325	29.30	.....	.....	.....	9.30	
Condurango.....G	10379	12.00 (40)	.....	.....	.....	11.23	
Condurango.....G	12682	10.86 (49)	.....	.....	.....	8.10	
Cotton Root Bark...W	11049	7.61	.....	.....	.....	6.30	
Cotton Root Bark...G	12094	5.30	.....	.....	.....	5.20	
Cotton Root Bark...G	12246	8.05	.....	.....	.....	5.10	
Cubeb.....W	11955	9.70	.....	.....	.....	6.00	7.67 per cent. of stems and foreign substances.
Cubeb.....W	11056	10.34	.....	.....	.....	5.17	
Cubeb.....W	11154	11.04	.....	.....	.....	6.38	12.71 per cent. of stems.
Cubeb.....W	11155	0.68	.....	.....	.....	4.00	
Cubeb.....W	11107	8.87	.....	.....	.....	11.89	
Cubeb.....P	11346	9.35	.....	.....	.....	7.99	
Cubeb.....P	11104	0.91	.....	.....	.....	10.39	
Curcuma.....P	11165	8.12	.....	.....	.....	6.30	
Curcuma.....P	11104	0.91	.....	.....	.....	6.99	
Curcuma.....P	11165	8.12	.....	.....	.....	6.42	
Damia.....G	13419	19.25 (65)	.....	.....	.....	18.91	Ash contained sand.
Damia.....G	13467	21.41 (65)	.....	.....	.....	8.06	
(Dittany) Cretan...W	12873	12.00	.....	.....	.....	12.95	24.5 per cent. unattached stem
Dogwood, Jamaica...G	11670	16.64 (65)	.....	.....	.....	11.50	
Dogwood, Jamaica...G	13119	10.37 (65)	.....	.....	.....	8.10	
Dogwood, Jamaica...G	13685	9.63 (65)	.....	.....	.....	13.03	
Dragon's Blood.....P	11701	74.35	(Acid No. 27.9)	.....	.....	8.71	Coloring properties fair.
Dragon's Blood.....P	13347	80.15	(Acid No. 3.3)	.....	.....	72.90	Coloring properties very poor.
Dragon's Blood.....P	12427	77.05	(Acid No. 5.5)	.....	.....	82.40	Coloring properties good.
Dragon's Blood.....P	13574	74.65	(Acid No. 61.6)	.....	.....	76.92	Contained rosin.
Dragon's Blood.....P	13575	65.55	(Acid No. 3.0)	.....	.....	82.80	Coloring properties fair.
Elm Bark.....P	10961	.....	.....	.....	.....	10.50	
Elm Bark.....P	12112	.....	.....	.....	.....	8.10	
Euonymus.....G	13105	18.73 (78)	.....	.....	.....	9.30	

Eupatorium.....G	12665	22.80 (49)	.....	.....	.....	9.97
Euphorbium.....P	11650	41.93	.....	.....	.....	44.25
Fraxineek.....P	12185	10.85	.....	0.50	.....	3.15
Fraxula.....P	11428	24.50 (38)	.....	.....	.....	5.24
Gamboge.....P	11763	76.36	.....	.....	.....	0.85
Gelsenium.....G	13423	2.05	.....	.....	.....	0.38
Gentian.....G	13421	40.88 (49)	.....	.....	.....	3.40
Gentian.....G	12403	33.40 (49)	.....	.....	.....	3.30
Gentian.....P	12404	37.70 (49)	.....	.....	.....	3.45
Gentian.....G	12653	34.13 (49)	.....	.....	.....	3.38
Ginger.....G	11381	3.83	.....	3.56	3.55	5.16
Ginger, Jamaica.....P	11660	4.98	.....	1.95	2.79	3.30
Ginger, Jamaica.....P	12405	5.50	.....	1.95	4.97	3.70
Ginger, African.....G	12656	6.23	.....	1.62	5.31	4.90
Ginger, African.....G	13083	6.20	.....	1.95	5.45	8.75
Glycerhiza.....G	11202	.....	.....	.....	.....	8.49
Glycerhiza.....P	11601	.....	16.50	.....	.....	4.34
Glycerhiza.....P	11602	.....	23.36	.....	.....	4.50
Glycerhiza.....G	11656	.....	16.80	.....	.....	8.60
Glycerhiza.....G	12813	.....	15.78	.....	.....	6.45
Guaiac.....W	11633	76.80	.....	.....	.....	4.00
Guaiac.....P	12479	70.06	.....	.....	.....	4.61
Guaiacum Wood.....G	13380	23.40 (70)	.....	.....	.....	0.90
Hellebore, Black.....G	10962	27.99 (70)	.....	.....	.....	17.88
Hellebore, White.....G	13581	31.15 (70)	.....	.....	.....	13.61
Hellebore, White.....P	12753	.....	.....	.....	.....	12.15
Hellebore, White.....P	13850	.....	.....	.....	.....	16.10
Helonias Dioica.....G	12784	28.19 (49)	.....	.....	.....	7.70
Helonias Dioica.....G	12785	28.97 (49)	.....	.....	.....	3.60
Helonias Dioica.....G	13074	31.36 (49)	.....	.....	.....	5.97
Hops.....G	11429	31.41 (49)	.....	1.85	17.19	8.10
Hops.....G	12371	34.53 (49)	.....	1.68	17.71	8.08
Hops.....G	13684	29.40 (49)	.....	0.72	12.45	12.01
Hydrangea.....G	13148	13.63 (49)	.....	.....	.....	8.35
Insect Powder.....	11565	10.71	.....	.....	4.43	4.83
Insect Powder.....	11566	11.40	.....	.....	6.70	4.93
Insect Powder.....	11567	9.39	.....	.....	3.71	5.78
Insect Powder.....	12361	14.05	.....	.....	7.95	5.85
Insect Powder.....	13585	12.25	.....	0.65	5.70	6.40
Juniper Berries.....P	11700	40.15 (49)	.....	1.27	15.0	3.25
Juniper Berries.....G	12777	28.12 (49)	.....	0.94	13.55	3.27

Alk. Aqueous Extract 29.1 per cent.  
Alk. Aqueous Extract 30.0 per cent.  
Alk. Aqueous Extract 30.4 per cent.  
Alk. Aqueous Extract 26.8 per cent.  
Alk. Aqueous Extract 25.8 per cent.

Alk. 0.056 per cent.  
Alk. 1.030 per cent.  
Alk. 0.836 per cent.

Contained few pollen grains.  
Normal pollen grains.  
Very few pollen grains.  
Large amount of grains and woody matter.

TABULATION OF ASSAYS—(Continued)

SAMPLE	Sample No.	Alcohol extract, Per cent.	Water extract, Per cent.	Ether extract Per cent.		Ash Per cent.	Remarks.
				Vol.	N. Vol.		
Kino.....W	11247	62.43	67.96	.....	.....	2.83	
Krameria.....G	13722	28.54 (49)	.....	.....	.....	1.35	
Lactucarium.....W	11245	44.21	27.82	4.45	47.33	6.71	
Lappa.....G	11708	24.60 (49)	.....	.....	.....	6.22	
Larkspur Seed.....W	11205	25.06	.....	13.49	30.58	6.55	2.06 per cent. of foreign substance.
Larkspur Seed.....W	11604	23.12	.....	.....	44.00	6.67	2.15 per cent. of foreign substance.
Larkspur Seed.....W	11841	19.52	.....	.....	34.14	6.53	1.66 per cent. of foreign substance.
Larkspur Seed.....P	12187	42.15	.....	3.42	39.98	6.25	
Larkspur Seed.....G	12787	44.75	.....	1.76	43.29	6.40	
Larkspur Seed.....W	12692	46.57	.....	7.2	42.67	5.19	1.2 per cent. of foreign substance.
Lobelia.....G	11481	18.42 (49)	.....	.....	.....	8.15	
Lupulin.....P	10832	.....	.....	.....	55.18	31.79	
Lupulin.....P	11082	.....	.....	.....	57.06	33.61	
Lupulin.....P	11828	.....	.....	.....	32.49	49.07	
Madder Root.....P	11779	19.77	27.06	.....	.....	20.02	
Madder Root.....P	11780	27.33	43.77	.....	.....	12.50	
Madder Root.....P	12138	24.80	23.90	.....	.....	28.70	
Madder Root.....P	13551	13.50	17.90	.....	.....	49.80	Contained sand.
Manna, Large Flakes.....P	11586	99.45 (67)	.....	.....	.....	0.57	
Manna, Small Flakes.....P	11587	98.21 (67)	.....	.....	.....	1.16	
Marrubium.....G	11758	18.16 (49)	.....	.....	.....	14.66	
Mastic.....W	11588	87.60	(Acid No. 53.78)	.....	98.38	0.29	
Mastic.....P	11639	86.60	(Acid No. 56.57)	.....	98.27	0.50	
Mastic.....W	11701	82.77	(Acid No. 58.50)	.....	98.26	6.15	
Mastic.....P	12680	91.26	(Acid No. 57.20)	.....	96.85	.....	
Mastic.....P	12933	81.10	(Acid No. 52.78)	.....	94.40	0.50	
Matico Leaves.....W	11998	15.79	.....	6.75	14.95	14.50	
Matico Leaves.....W	12322	16.50	.....	0.4	14.95	15.60	
Matico Leaves.....W	12833	16.80	.....	3.5	10.49	14.95	
Mullein.....G	12215	16.19 (49)	.....	.....	.....	15.28	
Mustard, Black.....P	10925	.....	.....	.....	15.60	5.04	
Mustard, Black.....P	11278	.....	.....	0.46	17.34	5.28	
Mustard, Black.....P	11309	.....	.....	0.96	23.47	4.77	
Mustard, Black.....P	11980	.....	.....	0.45	27.86	4.70	



TABULATION OF ASSAYS.—Continued.

SAMPLE	Sample No.	Alcohol extract Per cent.	Water extract, Per cent.	Ether extract Per cent.		Ash Per cent.	Remarks.
				Vol.	N. Vol.		
Saffron, Spanish.....	11454	.....	64.42	.....	.....	5.14	6.10 per cent. unattached styles.
Saffron, Spanish.....	11499	.....	60.27	.....	.....	4.51	21.75 per cent. unattached styles.
Saffron, Spanish.....	11491	.....	71.56	.....	.....	1.25	20.23 per cent. unattached styles.
Saffron, Spanish.....	11492	.....	64.00	.....	.....	5.92	7.75 per cent. unattached styles.
Saffron, Spanish.....	11078	.....	73.00	.....	.....	4.00	1.00 per cent. unattached styles.
Saffron, Spanish.....	12410	.....	60.70	.....	.....	5.61	9.50 per cent. unattached styles.
Sandalwood.....	13026	6.05 (70)	.....	.....	.....	5.58	
Sandalwood.....	13431	5.86 (95)	(Alcohol Extract 4.27 per cent. (70)	.....	.....	5.41	
Santonica.....	11944	22.30	.....	4.10	15.75	8.50	25 per cent. stems and foreign substances.
Santonica.....	12063	25.10	.....	4.90	11.35	10.25	21 per cent. foreign substances.
Santonica.....	12094	22.90	.....	5.00	13.55	8.75	32 per cent. stems and foreign substances.
Sarsaparilla.....	11070	17.90 (32)	.....	.....	.....	12.00	
Sarsaparilla.....	13566	15.75 (32)	.....	.....	.....	13.90	
Sassafras.....	11200	13.06 (70)	.....	0.30	3.14	20.15	
Sassafras.....	11228	20.72 (70)	.....	0.68	3.89	12.92	
Sassafras.....	11229	17.35 (70)	.....	0.53	2.22	40.57	
Sassafras.....	11230	10.68 (70)	.....	0.44	2.05	24.07	
Sassafras.....	11551	19.84 (70)	.....	0.97	2.12	17.57	
Sassafras.....	13874	33.75 (70)	.....	0.57	3.83	5.47	
Saw Palmetto.....	13422	20.26	.....	.....	.....	30.5	
Scoparius.....	13206	24.10 (49)	.....	.....	.....	2.95	
Senega.....	11446	33.22 (63)	.....	.....	6.23	6.74	
Senega.....	9739	37.90 (63)	.....	.....	8.48	6.04	
Senega.....	12392	33.75 (63)	.....	.....	8.68	3.98	
Senega.....	12911	30.56 (63)	.....	.....	.....	6.26	
Senega.....	13682	34.62 (63)	.....	.....	.....	6.57	
Senna, Alexandria.....	10826	.....	27.39	.....	.....	20.10	
Senna, Alexandria.....	11808	31.72 (49)	.....	.....	.....	10.53	

Senna, Alexandria.....	G	11809	20.59 (49)	.....	10.50
Senna, Alexandria Sifting..	G	12347	12.60 (49)	.....	0.42
Senna, Alexandria.....	G	12579	31.36 (49)	.....	9.00
Squaw Vine.....	G	12782	20.35 (40)	.....	11.43
Squaw Vine.....	G	13673	25.06 (49)	.....	6.93
Squill Cut.....	G	13283	.....	79.05	2.40
Staphisagria.....	G	13221	25.85	.....	21.80
Stillingia.....	G	9952	14.32 (49)	40	0.72
Stillingia.....	G	11054	11.32 (49)	.....	4.05
Stillingia.....	G	12383	11.99 (49)	.....	2.75
Stillingia.....	G	13078	13.58 (49)	.....	4.55
Sumach Berries.....	G	11480	10.59 (49)	.....	2.09
Sumbul.....	G	10937	20.23 (70)	.....	4.72
Taraxacum.....	G	11382	32.14 (49)	.....	11.40
Taraxacum.....	G	12709	37.96 (49)	.....	8.37
Taraxacum.....	G	11697	.....	48.62	3.92
Triticum Cut.....	G	10457	33.21 (30)	.....	4.15
Uva Ursi.....	W	12957	35.06 (20)	.....	2.91
Uva Ursi.....	G	11575	22.32 (49)	.....	16.46
Valerian.....	W	12038	18.50 (73)	1.90	2.08
Valerian.....	G	12407	10.69 (73)	0.50	1.70
Valerian.....	P	13390	18.40 (76)	0.70	3.30
Valerian.....	G	11579	35.09	0.25	26.40
Verbasum Flowers.....	W	11522	20.96 (65)	0.38	2.68
Viburnum Opulus.....	G	12781	20.40 (65)	.....	3.89
Viburnum Opulus.....	G	13076	22.30 (65)	.....	3.10
Viburnum Opulus.....	G	9953	16.88 (65)	.....	3.39
Viburnum Prunifolium.....	G	10023	17.48 (65)	.....	9.01
Viburnum Prunifolium.....	G	12780	23.12 (65)	.....	4.43
Viburnum Prunifolium.....	G	13118	23.15 (65)	.....	4.40
Wild Yam.....	G	11724	18.32 (49)	.....	4.80
Wintergreen.....	G	10499	16.38 (70)	.....	3.84
Wintergreen.....	G	12476	25.04 (70)	1.18	3.44
Zanthoxylum.....	G	13166	23.28 (65)	.....	5.35
Zanthoxylum.....	W	13478	15.35	0.25	6.80
Zanthoxylum.....	W	13479	18.95	0.25	4.80
Zanthoxylum.....	W	13480	18.22	0.25	10.75
Zanthoxylum.....	W	13481	14.90	0.10	10.35
Zanthoxylum.....	W	.....	.....	.....	5.40
Zanthoxylum.....	W	.....	.....	.....	12.90
Zanthoxylum.....	W	.....	.....	.....	9.65

The methods for assaying the drugs reported in this paper are essentially the same as previously given.

For further particulars the reader is referred to the first paper appearing in the October, 1912, number of this JOURNAL.

The results of the assays are given in the table on pp. 436-443. Abbreviations, etc.: W.—Whole drug; P.—Powdered drug; G.—Ground drug. Where the alcoholic menstruum used in determining the anhydrous alcohol extract was of a percentage other than 95 per cent. absolute alcohol, the percentage is indicated by the figure in brackets; for example, 20.3 (49), 32.6 (63) indicating 49 and 63 per cent. absolute alcohol, respectively.

*Agar-Agar*—Four samples contained ash 8.23, 4.8, 4.5 and 4.4 per cent. respectively.

*Gambir*—Fifteen samples: Alcohol Extract—Minimum 63.30 per cent., maximum 87.00 per cent., average 78.6 per cent. Aqueous Extract—Minimum 61.7 per cent., maximum 82.75 per cent., average 77.95 per cent. Ash—Minimum 3.40 per cent., maximum 8.48 per cent., average 5.55 per cent.

*Ipecac*—Eight samples: Ash minimum 3.40 per cent., maximum 4.63 per cent., average 4.10 per cent.

*Jalap*—Seven samples: Ash minimum 0.62 per cent., maximum 1.77 per cent., average 1.29 per cent.

*Lycopodium*—One sample contained 8.61 per cent. ash, which was chiefly calcium carbonate.

*Salap*—One sample ash 2.24 per cent.

*Taraxacum*—One sample submitted consisted of approximately 50 per cent. chicory.

ANALYTICAL DEPARTMENT,  
SCHIEFFELIN & Co., New York.

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## THE DETECTION OF EMODIN-BEARING DRUGS IN PRESENCE OF PHENOLPHTHALEIN.

By L. E. WARREN.

Phenolphthalein, either alone or in mixture with other drugs, is a constituent of a number of nostrums which are sold as laxatives. The separation and identification of phenolphthalein in medicines is usually accomplished readily, but its presence may interfere with the



identification of other drugs. This is likely to be the case with cascara, senna, and other emodin-bearing drugs. Ordinarily the emodin-bearing drugs as a class would be detected by shaking the faintly acidified extracts with benzol and washing the solvent first with water, which is discarded, and then with very dilute ammonia water.<sup>1</sup> In presence of emodin the ammoniacal layer becomes red, the depth of color and shade depending somewhat upon the amount of emodin present and the source of the drug from which obtained. This test cannot be used in presence of phenolphthalein because this substance behaves like emodin. This holds true in spite of the great insolubility of phenolphthalein in water,<sup>2</sup> for if a solution containing this substance be acidified, diluted with several times its volume of water and filtered, the filtrate will become strongly colored purplish-red on the addition of ammonia water or of potassium hydroxide or sodium hydroxide solution. Or if the acid filtrate be shaken with benzol, the aqueous layer discarded, and the solvent washed with either of these alkaline solutions, the purplish-red color appears at once. Unless the quantity of phenolphthalein be very small the color produced by it with the alkalis will hide or obscure that of any emodin alkali compounds that may be present.

Under certain conditions, however, the color produced by phenolphthalein and an excess of the fixed alkali hydroxides gradually disappears, owing to the formation of the trimetallic salt of phenol-

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<sup>1</sup> Bornträger: *Z. anal. Chem.*, 19, 165 (1880).

<sup>2</sup> According to McCoy (*Am. Chem. Jour.*, 31, 503, 1904), the maximum solubility of phenolphthalein in water is approximately a ten-thousandth-normal solution. This is equivalent to about 0.0032 Gm. of the substance in 100 c.c. This conclusion was reached after approximate determinations had been carried out by two methods. In one 0.0318 Gm. of purified phenolphthalein was boiled with 1200 c.c. of water. On cooling no deposit formed, indicating a solubility greater than twelve-thousandth-normal. In the other known amounts of tenth-normal phenolphthalein (in alcohol) were added to 100 c.c. of five-hundredth-normal ammonia water and the solution neutralized by the addition of 2 c.c. of tenth-normal hydrochloric acid. With 0.5 c.c. of the phenolphthalein solution the resultant solution contained a precipitate of phenolphthalein; with 0.3 c.c. the solution was turbid; with 0.2 c.c. faintly turbid; and with 0.1 c.c. clear, although a slight deposit formed on standing over night. This indicated a solubility of about ten-thousandth-normal, corresponding to 0.00318 Gm. per 100 c.c. On the other hand, Zotier (*Bull. soc. chim.* [4], 7, 993, 1910), from an average of thirty determinations (method not stated), gives the solubility of phenolphthalein in water as about 0.0092 Gm. in 100 c.c.

phthalein, leaving the solution colorless. On the other hand, the color of the alkali compounds with emodin is more stable, sometimes lasting for several days.\* An attempt was made to differentiate by this test between phenolphthalein and emodin when in mixture, but the results were not very satisfactory. If applied to a mixture of phenolphthalein and an extract of an emodin-bearing drug, obtained by extraction with alcohol and evaporation of the solvent, the extracted coloring matter renders the test worthless. If applied to a benzol, chloroform, or ether extract, the confusion of colors renders positive identification doubtful. However, if the red color of the strongly alkaline solution disappears the test is a valuable confirmation of the absence of most of the emodin-bearing drugs. If the color persists after standing for several hours, the presence of an emodin-bearing drug is presumptive. A method seemed desirable by which the phenolphthalein might be removed from such mixtures, thus leaving the emodin free to be tested for in the usual way. Of the several methods used for its quantitative determination, that proposed by Kollo,<sup>3</sup> by which the substance is precipitated as tetraiodophenolphthalein,<sup>4</sup> seemed the most promising.

Some tests were first made with a preparation known to contain phenolphthalein (most of which was in suspension) and an emodin-bearing drug extract.

The following method was used:

The preparation, which was in the form of a syrup, was diluted with water, faintly acidified and filtered to remove most of the phenolphthalein. The filtrate was neutralized with ammonia water, evaporated to a very thick syrup, and the warm syrup extracted with acetone (which had been rendered slightly acid by hydrochloric acid) by stirring with successive small portions of the solvent and decanting from the residue. In this case acetone was found a more suitable solvent than either chloroform or ether, as it formed less troublesome emulsions. In preparations that do not form emulsions ether extracts are more satisfactory for the subsequent manipulations. The acetone fractions were united, evaporated to dryness on the water-bath, the

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\* Experiments have shown that if ether extracts from small amounts of rhubarb be heated on the water-bath for three hours with 50 per cent. sodium hydroxide solution the red color is not destroyed.

<sup>3</sup> *Ap. Ztg.*, 24, 283 (1909).

<sup>4</sup> Tetraiodophenolphthalein was first described by Classen and Loeb (*Ber.*, 28, 1603, 1895).

residue twice moistened with alcohol and evaporated in order to remove the last trace of acetone. The residue was taken up in diluted sodium hydroxide solution, the solution filtered, and a slight excess of iodine test solution added, followed, after a few minutes, by a slight excess of hydrochloric acid. The container was cooled for an hour in a water-bath having a temperature below 15° C. and the contents filtered. By this treatment the phenolphthalein was precipitated as tetraiodophenolphthalein, a substance which is very insoluble in water. The precipitate on the filter was washed with water several times, a yellow solution being produced. The filtrate and washings were united, the solution treated with a slight excess of sodium sulphite to remove free iodine, and the solution shaken with chloroform. The chloroform was evaporated and the residue treated with dilute solution of sodium hydroxide. By this treatment the anthracene purgatives give red colors which vary in shade, depending somewhat upon the source of the emodin. Preparations containing phenolphthalein alone give no red color, or at most a faint purplish-red, which soon fades if a considerable excess of the alkali be added.

Briefly stated, the method consists in treating an acetone or ether extract of the substance with sodium hydroxide solution, adding iodine solution, followed by hydrochloric acid, removing the tetraiodophenolphthalein by filtration after standing, shaking out the filtrate with chloroform after adding a sulphite to remove excess of iodine, evaporating the chloroform, and treating the residue with sodium hydroxide solution.

As controls the test was carried out with the fluidextracts of cascara and rhubarb, a mixture of the fluidextracts of senna and licorice, a trade preparation stated to contain senna, a mixture containing aloes and phenolphthalein, and a trade preparation claimed to be a form of bitterless cascara. The residue from the fluidextract of cascara gave a dark red color with a faint brownish tinge, that from rhubarb a deep red with a suggestion of purplish, that from the senna-licorice mixture a somewhat lighter red with a faint suggestion of yellowish (the licorice did not interfere), that from senna alone a color similar to that from the mixed senna and licorice, that from the aloes and phenolphthalein a faint reddish-yellow, and that from the bitterless cascara preparation a color similar to that given by the fluidextract of cascara. The test with aloes was carried out several times, but with results that were not entirely satisfactory. The colors given for the several drug residues do not differ from each

other sufficiently to positively identify the source of the drug, yet they should prove of considerable value as confirmatory evidence. The light red from senna would not ordinarily be mistaken for the deeper red of cascara or of rhubarb, nor the faint reddish-yellow of aloes for any of the others, particularly if controls be carried out. In some instances, on standing, a reddish, flocculent precipitate was formed in the alkaline solutions as finally obtained. On its removal by filtration the filtrate became lighter in color. In the test with the aloes-phenolphthalein mixtures the filtrate became of a reddish-yellow color. On the whole the test is much less satisfactory for aloes than for the other drugs tested.

While these experiments were in progress Bailey<sup>5</sup> published a method of distinguishing chrysophanic acid of rhubarb from phenolphthalein. By his method the dealcoholized, faintly acidified preparation is shaken with ether, and the solvent layer washed with very dilute ammonia water. The alkaline solution is allowed to stand over night, by which the colored compounds of hæmatoxylon and curcuma, if present, fade. The solution is then acidified and shaken with ether. Only chrysophanic acid and phenolphthalein pass into the solvent. The ether is evaporated and the residue boiled with zinc dust and potassium hydroxide solution until the red color has entirely disappeared. By this treatment chrysophanic acid is reduced, the solution becoming yellowish, and phenolphthalein is reduced to phenolphthalin. The solution is diluted with water, or a drop of hydrogen peroxide solution is added. A cherry-red color appearing at once indicates chrysophanic acid. Under these conditions phenolphthalin is not oxidized.

Bailey did not apply his method to cascara or to aloes, but implies that it might be used on senna preparations. We have applied the method to the fluidextracts of senna and cascara, to each of which some alcoholic solution of phenolphthalein had been added. In each case the result was satisfactory. It was found necessary to boil the alkaline zinc-dust mixture for some time in order to completely destroy the red color. It was also found that exposure of the boiled solution to the air, as in filtration, was generally sufficient to restore the color to the substance. When the test was applied to Barbadoes aloes the red color given on the addition of hydrogen peroxide solution was slow to appear and was masked considerably by yellow coloring matters. To the limited extent that comparison tests have been

<sup>5</sup> *Jour. Ind. Eng. Chem.*, 6, 320 (1914).

carried out it does not appear that either method has any marked advantage over the other. If hæmatoxylon or curcuma be present, results may be obtained more quickly by the proposed iodine method, since the colors from these substances are destroyed (or removed) by the iodine treatment, hence it is unnecessary to wait over night for the destruction of the coloring matters by treatment with ammonia.

*Summary.*—The presence of phenolphthalein in medicines interferes with the detection of the emodin-bearing drugs.

Phenolphthalein may be removed by treating the ether (or acetone) extract with sodium hydroxide and iodine solutions, adding hydrochloric acid and filtering.

After removal of the phenolphthalein the emodin may be detected in the usual way, using a fixed alkali hydroxide for its solution.

The method was tried on several emodin-bearing drugs and gave satisfaction, except in the case of aloes.

LABORATORY OF THE AMERICAN MEDICAL ASSOCIATION.

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## RED GUM.

By JOHN K. THUM, Pharmacist at German Hospital, Philadelphia.

*Eucalyptus rostrata* yields the extract Australian Kino, and more popularly known by the name "Red Gum." The latter is found on the market, pharmaceutically, in the form of troches and in a fluid form, misleadingly termed by the manufacturers a fluidextract.

Like Kino of the U. S. P., it contains considerable tannin, which makes it extremely valuable as an astringent. The so-called fluid-extract has obtained some vogue among throat specialists as a local application in place of the well-known Glyceritum Tannin, it being much more agreeable and pleasant to the patient, and just as efficient as the latter preparation.

While all the manufacturers who market a fluid form of red gum have it listed in their price lists as a fluidextract, some have an asterisk placed alongside the word, and on referring to the footnote one finds these words: "those fluids which do not represent the crude drug, minim for grain"; which is a tacit confession that it is impossible to make a 100 per cent. solution of this drug.

On looking over the literature relating to this drug—and the literature, by the way, is scant—one is informed that it is soluble in cold water to the extent of 80 to 90 per cent. This is wrong. It is

extremely doubtful if as much as 30 per cent. is soluble in cold or even boiling water. My experience leads me to believe that less than 20 per cent. of the drug is soluble in boiling water, and that it refuses to remain in solution without the addition of varying amounts of glycerin; without this addition gelatinization always results. My experience also showed that the use of alcohol in effecting solution is unnecessary, or at least less effective than a menstruum consisting of water and glycerin. Heat must be used. I found that after shaking 20 parts of the powdered drug with 80 parts of cold water, at intervals, for twelve hours, two parts of drug remained in solution. By heating in a flask on a water-bath for 15 minutes and frequently shaking, about 10 per cent. is dissolved. Unfortunately, after a few days a jelly-like mass results. This, however, as mentioned above, can readily be overcome, or rather avoided, by the addition of glycerin or, better still, by heating on a water-bath with equal parts of glycerin and water.

. After more or less experimentation, which I need not recount here, I evolved the following formula and method of procedure, which seems to meet all the requirements of those physicians who wish to use red gum as a local application:

Red Gum, powdered .....	200 Gm.
Glycerin .....	250 Cc.
Water, a sufficient quantity to make..	1000 Cc.

Mix the glycerin with five hundred cubic centimetres of water, and triturate the powdered red gum with sufficient of the mixture to produce a smooth paste. Transfer this to a flask by the aid of the remainder of the mixture of glycerin and water and heat on a water-bath for one hour; filter through purified cotton, keeping the funnel well covered. Finally, pass sufficient water through the filter to obtain one thousand cubic centimetres of fluid.

## ANALYSES OF TWO ECHINACEA ROOTS.

By F. W. HEYL and J. F. STALEY.

A review of the literature indicates that a further chemical study of Echinacea, particularly of *Brauneria angustifolia*, might be of some value in offering evidence concerning the conflicting views concerning the pharmaceutical value of this plant.

This root has been stated<sup>1</sup> to contain minute quantities of an inactive alkaloid. Its supposed medicinal activity is ascribed to the presence of a resin. Lastly, in describing the pharmacognosy of Echinacea,<sup>2</sup> Henry Kraemer and Maud Sollenberger have found inulin.

Despite the unfavorable report of the American Medical Association, Council on Pharmacy and Chemistry,<sup>3</sup> this plant is used to some extent, and a review of the meagre chemical literature indicates that more experimental evidence is required before forming a conclusion concerning its value pharmaceutically.

In this brief paper we report the results of the proximate analyses of two species, and further work is in progress upon the more important *Brauneria angustifolia*. The sample of *Brauneria purpurea* was obtained upon the market as a sample of Echinacea.

#### EXPERIMENTAL.

The material for this investigation consisted of the roots of two species of the genus *Brauneria* (*Echinacea*) of the family Compositæ, (a) *Brauneria angustifolia* (D. C.) Heller, the narrow-leaved purple cone flower, and (b) *Brauneria purpurea* (D. C.) Britton, the purple cone flower.

The *Echinacea* of the U. S. Dispensatory,<sup>4</sup> in so far as it applies to "*Brauneria pallida* (Nutt.) Britton," is a confusion of two species. The "*Echinacea angustifolia* D. C." there considered a synonym of the above (*B. pallida*) is now known to be a separate and distinct species, *Brauneria angustifolia* (D. C.) Heller, and has from our observations furnished most of the Echinacea of the market. It is this species which furnishes the principal material under investigation. The recognition of this confusion leaves *Brauneria pallida* (Nutt.) Britton as a species of good standing.<sup>5</sup>

The roots of *Brauneria angustifolia* were collected for us in the rough gravelly prairie land of north central Kansas. The *Brauneria purpurea* was said to have been collected in Missouri.

The roots of *Brauneria angustifolia* were received at the labora-

<sup>1</sup> C. G. Lloyd, *Eclectic Med. Journal* (1897).

<sup>2</sup> AMERICAN JOURNAL PHARMACY, 83, 315 (1911).

<sup>3</sup> *Journal A. M. A.*, vol. 53, 1836 (1909).

<sup>4</sup> U. S. Dispensatory, p. 1476 (19th Ed.).

<sup>5</sup> Robinson, B. L., and Fernald, M. L.: "Gray's New Manual of Botany," 1908, p. 832.

Britton, N. L., and Brown, A.: "Illustrated Flora," 1913, p. 476.

tory in the green condition, and after careful identification by Dr. L. H. Harvey, to whom we are indebted for the botanical work, were ground while still fresh. A large quantity of this material was transferred to percolators and exhausted with 95 per cent. alcohol, as will be described later.

A small sample was air-dried, and then ground and sieved. This was used for the proximate analyses. The *Brauneria purpurea* was received in the air-dried condition and ground and sieved by us.

The roots were quantitatively extracted, with the following results:

Extract.	<i>B. angustifolia.</i>	<i>B. purpurea.</i>
Ligroin (35°-55°) .....	0.77	0.93
Ether (110°) .....	1.26- 1.18	1.61
Alcohol (110°) .....	19.70-19.94	18.28

• The proximate analyses were conducted in accordance with the usual <sup>6</sup> methods, and gave the results tabulated in the following table:

	<i>B. angustifolia.</i>	<i>B. purpurea.</i>
Moisture .....	10.90	10.18
Starch .....	Absent	Absent
Pentosans .....	15.6 15.1	15.6
Crude Fiber .....	24.77, 24.46	29.65, 29.51
Protein .....	6.54, 6.96	5.31, 5.17
Ash .....	7.76	6.93

The residues left after extracting with alcohol were next digested with cold water, for the purpose of ascertaining if any dextrin-like substances were present. The residue left after extracting ten grammes of the root of *B. angustifolia* with alcohol, when digested with cold water yielded considerable soluble material. The aqueous extract was quantitatively made to a volume of 20 c.c. (2 c.c. = 1.0 gramme root). Four cubic centimetres of this was diluted to 50 c.c., and 25 c.c. of this solution showed no reducing action on Fehling's solution. The other 25 c.c. was hydrolyzed with hydrochloric acid, whereupon it showed the presence of 0.0682 Gm. lævulose, equivalent to 6.14 per cent. of "inuloid-like" material.

The remainder of the original aqueous solution (16 c.c.) was made up to a volume of 18 c.c. with lead subacetate. A heavy precipitate was removed by filtration. This filtrate then has a concentration of 0.4445 Gm. of the root per cubic centimetre. It showed a rotation of  $-2.3^{\circ}$ , Ventzke in a 1 dcm. tube. Assuming a specific rota-

<sup>6</sup> U. S. Dept. Agr. Bur. of Chem. Bull. 107 (Revised).



tion of  $-32.46^{\circ}$ , which is that recorded<sup>7</sup> for "sinistrin," this would represent 5.55 per cent. of the plant. The solution, freed from lead and hydrolyzed, showed the presence of a quantity of levulose equivalent to 5.94 per cent. "inuloid-like material," indicating the non-carbohydrate nature of the lead subacetate precipitate.

Inulin was determined by the method of Dragendorff<sup>8</sup> wherein the plant is extracted with water  $55^{\circ}$  to  $60^{\circ}$  and the inulin precipitated with three volumes of alcohol. The inulin was determined by determining the levulose formed when this precipitate was hydrolyzed. A correction of 0.1 gm. per 100 c.c. of the volume of the filtrate was made for the solubility of the inulin. Whether or not this inulin precipitate included any of the material determined as "inuloid" was not established. The following table gives the results of the various estimations of alcohol insoluble carbohydrates:

	<i>B. angustifolia.</i>	<i>B. purpurea.</i>
Inulin .....	5.9%	not determined
Inuloid <sup>9</sup> .....	5.94, 6.14%	9.16%

*Determination of the Alcohol Soluble Carbohydrates by Polariscopic methods.*—One hundred grammes of *B. angustifolia* were completely extracted with hot alcohol. The combined alcoholic extracts were concentrated under diminished pressure to a volume of 200 c.c. An aliquot of this solution, equivalent to 74 grammes of the root, after the complete removal of the alcohol, was taken up in water, clarified with an excess of lead subacetate, and made up to a volume of 100 c.c. This solution showed a rotation of  $-2.2$  in a 2 dm. tube at  $22^{\circ}$  C.

Fifty cubic centimetres of the filtrate from the lead subacetate precipitation was freed from the lead and inverted by standing with 5 c.c. hydrochloric acid for 24 hours. The solution was neutralized and made up to 100 c.c. It showed a rotation of  $-13.25^{\circ}$  in a 2 dm. tube at  $22^{\circ}$  C., and of  $-6.8^{\circ}$  at  $86^{\circ}$  C. in a 2 dm. tube. These readings are on the Ventzke scale.

Converting these readings to the calculated rotations of a normal solution (26 Gm. in 100 c.c.), we have: direct reading at  $22^{\circ}$  C. of  $-0.77^{\circ}$ ; invert at  $22^{\circ}$  C. of  $-9.31^{\circ}$ ; and invert reading at  $86^{\circ}$  C. of  $-4.78^{\circ}$ . The percentage of sucrose calculated by Clerget's formula

<sup>7</sup> Dragendorff, "Plant Analysis," p. 67.

<sup>8</sup> "Plant Analysis," p. 87.

<sup>9</sup> "Biochem. Handlexikon," 2, 189.

is 6.5 per cent. The percentage of laevulose calculated on the basis of the change in rotation of the inverted solution due to change in temperature is 3.99 per cent.<sup>10</sup>

The following table includes the results of the quantitative work carried out upon the alcohol extract, which was examined for sucrose and hexose sugars, and for resin (insoluble in water) :

	<i>B. angustifolia.</i>	<i>B. purpurea.</i>
Resin .....	1.84	2.00
Sucrose .....	6.92	3.40
Reducing sugars .....	3.65, 3.52, 3.80	3.41

The roots were examined for alkaloids. Of each species we used duplicate ten-gramme samples for assay. When examined by the method which is official for belladonna root,<sup>11</sup> residues were obtained from *B. angustifolia* weighing 0.0054 and 0.0077 gramme. From *B. purpurea* the weights found were 0.0086 and 0.0063 gramme. These residues were not alkaloidal, as they failed to neutralize any N/50 acid, and the slightly acid solutions gave no precipitate with Mayer's reagent.

In order to affirm this point 200 grammes of *Brauneria angustifolia* were exhausted with Prollius' <sup>12</sup> solution by percolation. The percolate was thoroughly extracted with several portions of dilute sulphuric acid, and from this acid solution we were able to obtain neither an alkaloidal extract nor even a precipitation test with Mayer's reagent. We conclude, therefore, that no alkaloid sufficiently basic to be extracted by the ordinary methods is present in this drug. This, however, does not exclude the possibility of the presence of choline or allied substances. The recent work of Power and Browning <sup>13</sup> in isolating choline from dandelion root makes this a possibility worthy of note. *Brauneria purpurea* was not further studied in this connection.

*Volatile Oil in B. angustifolia.*—A portion of the fresh roots equivalent to 3.7 kilogrammes air dried was distilled with steam until the distillate was free from volatile oil. The first runnings were very slightly turbid and carried the odor characteristic of the drug. The

<sup>10</sup> "Commercial Organic Analysis," Allen, vol. I, p. 356 (1908). The observed rotations of the normal solution are about 1.5° to the left greater than those calculated for a mixture of laevulose and sucrose.

<sup>11</sup> U. S. Disp., 19th Ed., p. 228.

<sup>12</sup> Alcohol 8 c.c., ether 88 c.c., ammonia (10 per cent.) 4 c.c.

<sup>13</sup> *J. Chem. Soc.*, 101, 2411 (1912).

oil separated in the usual manner weighed 1.4 Gm. It was amber colored and had a powerful odor. This is equivalent to 0.04 per cent. of the air-dried drug.

*The resin*, to which the medicinal properties are ascribed, was prepared from a quantity of the fresh drug, corresponding to 33.3 kilogrammes of air-dried drug. This drug was exhausted by percolation with alcohol, the percolate (260 litres) was concentrated by distillation under diminished pressure to a volume of 11.5 litres. This concentrated alcoholic solution, from which a fatty layer separated in considerable quantity, was mixed with about 20 litres of distilled water, whereupon the precipitation of the resin was complete. After continued agitation for the purpose of thoroughly washing the resin, and long standing, the resin separated above a clear, reddish-brown aqueous layer. By siphoning, most of the aqueous layer could be separated from the resin. It was noticed that a very slight intermediate zone between the resin layer and the aqueous layer contained crystalline material. This was separated by mechanical means and in very small quantity, and crystallized from 95 per cent. alcohol. It proved to be an impure phytosterol, crystallizing in the characteristic laminae, melting at about 131° to 136° indefinitely, and giving the usual color reactions. It was returned to the resin.

The resin was finally washed with water, taken up in alcohol, and then dried in a vacuum. The weight was 628 Gm., equivalent to 1.88 per cent. It is a brownish-yellow resin, and if dissolved in alcohol forms an amber-colored solution, which yields no crystalline deposit. It is possible, however, to obtain in the first fraction a *green* resinous deposit, which differs from the resin proper, which has the characteristic taste of the root. The material was brought into one fraction, taken up in purified sawdust, and extracted with the following results:

	Gramme.
Ligroin extract .....	222.0
Ether extract .....	107.0
Chloroform extract .....	180.0
Ethyl acetate extract .....	35.0
Alcohol extract .....	70.0
Total .....	614.0

We are studying these extracts as well as the water-soluble extract in more detail.

## PROPOSED U. S. P. IX LIMITATIONS FOR THE ASH CONTENT OF DRUGS.

By M. I. WILBERT, Washington, D. C.

The figures given in the second instalment of abstracts of proposed new descriptions and standards for the drugs of vegetable and animal origin to be included in the U. S. P. IX (*J. Am. Pharm. Assoc.*, 1914, vol. 3, pp. 359-416) suggest a comparison with other available data as a basis for comment and criticism. Among the newer pharmacopœias the German, Austrian, Swiss, and Dutch appear to include ash limitations more frequently than do any of the corresponding books of other countries, and these four books have been selected as being fairly representative of the general requirements made in European pharmacopœias.

The quotations designated "recent literature" are compilations of the maximum and minimum figures given by various authors referred to in recent numbers of the Hygienic Laboratory Bulletins, embodying the Digest of Comments on the Pharmacopœia of the United States of America and on the National Formulary, for the calendar years 1909 to 1912, inclusive. These figures suffice to indicate the probable extremes of the ash content of drugs found in commerce at the present time, and reflect actual conditions so far as these have been reported.

A casual survey of the figures presented in the appended table suggests that a few of the root drugs, like apocynum, cimicifuga, pyrethrum, and spigelia, are not sufficiently well known abroad to warrant their recognition. Other drugs, like sweet almonds, physostigma, musk, and vanilla, do not appear to vary sufficiently to justify systematic records being made of their ash content, or, as in the case of musk, more particularly, are so expensive that the determination of the ash content is not generally adopted as a means of determining the purity or quality of the drug.

Among the figures that may be considered as being comparatively low are those for asafœtida, ipecac, and vanilla. The first of these drugs frequently contains very much more foreign matter than would be permissible under the proposed limitations. This foreign matter is present to a considerable extent, at least, because of the methods employed in collecting asafœtida, and it is questionable, indeed,

whether the inclusion of earthly impurities is not preferable to the now frequently practised adulteration or even substitution of asafoetida by other gum resins which, while they serve to increase the alcohol soluble material and reduce the ash content of the drug as offered, are quite foreign to and do not contain any appreciable quantity of the odorous principles found in true asafoetida.

The maximum ash content permitted for ipecac appears to be somewhat low, certainly lower than is the maximum recognized in other pharmacopœias. The same is true of vanilla, and in connection with this drug there is some question as to whether the ash content limitation for the whole drug is really of value or is necessary.

The drugs for which the ash content limitation appears to be rather high are much more numerous and include aloes, cantharides, belladonna leaves, colocynth, coriander, gambir, glycyrrhiza, guaiac, linseed, lupulin, myrrh, squills, mustard, stramonium, strophantus, taraxacum, valerian, and ginger.

A comparison of the proposed limitation for the ash of aloes with the limitations found in foreign pharmacopœias suggests the possible intent of providing for the rather inferior Asiatic or Moka aloes usually sold as Socotrine aloes, which has been found to contain rather large quantities of foreign material. A reasonably pure inspissated juice of the aloe plant when prepared in a cleanly method should readily comply with the requirements made in the German, Swiss, and Netherlands pharmacopœias.

The ash content for cantharides, while it agrees with the limitations included in the Dutch pharmacopœia, is, nevertheless, higher than need be. A number of careful investigators have asserted that a drug of good quality should contain less than eight per cent. of ash.

The proposition to permit 20 per cent. of ash in belladonna leaves appears to be inordinately liberal when compared with the limitation of 10 per cent. of ash for digitalis. Belladonna has a comparatively smooth leaf that would hold little or no sand or dust, while the digitalis leaf, being hairy, is much more readily contaminated by, and is more difficult to rid of, adhering sand and dirt. The figures reported in literature also suggest the desirability of some additional leeway for digitalis and the lack of any serious need for so high an ash content for belladonna leaf.

Colocynth is another drug that appears to have been given a rather high limit and one for which a minimum requirement of ash might be considered in view of the fact that the seed of colocynth has

been found to contain, on the average, much less ash than does the pulp.

Gambir varies considerably in its composition, and, being an extract, is not infrequently contaminated by the deliberate addition of sand and dirt. A number of observers in this country have stated that 6 per cent. of ash should not be exceeded by a drug of good quality, and this would in a general way conform with the limitations made for the closely related drug, catechu, in foreign pharmacopœias.

Lupulin is another drug that has rather a liberal allowance for ash, and, while it is true that the maximum permitted in Austria and Switzerland is usually exceeded by the commercially available product, it has, nevertheless, been repeatedly shown that commercial lupulin can readily be freed from contaminating sand and dirt to such an extent as to bring it below the 10 per cent. limit for ash, and that absolutely pure lupulin obtained directly from the strobiles of the hop will comply with the Dutch pharmacopœial limitation of 6 per cent.

The proposed ash content for squill, while it agrees with the maximum permitted in the Austrian pharmacopœia, appears to be unnecessarily high, when one considers the nature of the drug and the lack of need for providing for inorganic impurities.

The ash content limitations for the several seeds, like anise and fennel, while in accord with the limitations set in foreign pharmacopœias, are generally higher than the figures included in a recent regulation promulgated by the Bureau of Chemistry for these drugs when entered for imports.

The proposition to include limitations for ash insoluble in diluted hydrochloric acid, in connection with the several spices and with senna, while thoroughly well established in the trade, is rather a novel one in pharmacopœial work, and there may be considerable difference of opinion as to the desirability of including such an additional complicating requirement at this time.

Taken as a whole, it must be said that the proposed limitations for ash, while many, are reasonably conservative and comply fairly well with conditions as they exist in the drug market at the present time. Some further comparative study of the requirements, however, should prove interesting and will no doubt lead to the revision of the figures in connection with at least a few of the drugs referred to.

TABLE SHOWING PROPOSED U. S. P. LIMITATIONS FOR ASH COMPARED WITH REQUIREMENTS INCLUDED IN THE GERMAN, AUSTRIAN, SWISS, AND NETHERLANDS PHARMACOPŒIAS, AND THE VARIATIONS REPORTED IN RECENT LITERATURE.

	U. S. P. IX.	German V	Austrian VIII	Helvetian IV	Netherlands IV	Recent literature
Acacia .....	4	5	3	4	4	1.23- 3.64
Aconitum .....	6			6		3.6 - 6.
Agar-agar .....	5					2.6 - 4.
Aloe .....	4	1.5	1	1.5	1.5	0.65- 5.65
Althæa .....	8		6	6	3-7	4.6 - 7.31
Amygdala Dulcis .....	4					
Amylum .....	0.5	1		0.5	1	0.05- 0.27
Anisum .....	10	10	10	10		5.6 -18.46
Apocynum .....	9					3-4
Arnica .....	9		8			6.2 -11.5
Asafoetida .....	15	15	10	20	10	5. -63.70
Aspidium .....	3		3			2.2 - 5.44
Aurantii Amari Cortex	7		6	7		3.7 - 5.5
Belladonnæ Folia ....	20	15	15	15		2.35-23.5
Belladonnæ Radix ....	7		6	7		6.07- 7.84
Benzoinum .....	2	2	2	1.5	2	1.2 - 3.8
Buchu .....	4					4.2 - 5.80
Calumba .....	8		6	8		4.8 - 8.2
Cambogia .....	2					0.5 -18.0
Cannabis .....	15		15			6.0 -14.44
Cantharis .....	9	8		8	9	6.5 -10.29
Capsicum .....	1*	6.5	6.5	6.5		4.3 - 6.6
Cardamomi Semen ....	8		10	8	8	3.7 - 9.2
Carum .....	8		7	8		5. -11.9
Caryophyllus .....	0.5*	8	8	7	6	5.4 - 7.3
Cimicifuga .....	10					4.87- 9.65
Cinnamomum Saigon- icum .....	2*	5		5	8	1.30- 5.6
Cinnamomum Zeylan- icum .....	2*		5	5		3.3 - 6.83
Coccus .....	6			6		3.28- 9.41
Colchici Semen .....	8		8			2.4 - 3.5
Colocynthis .....	15		7			3.60-13.03
Condurango .....	12					5.26-16.71
Coriandrum .....	7.5		7			4.55- 8.10
Cubeba .....	8	8		8	10	
Digitalis .....	10		10	10		4.6 -18.5
Ergota .....	5			5	5	2.6 - 4.3
Fœniculum .....	10	10	10	10		7. -23.75
Frangula .....	6		5			3.7 - 6.5

\*Ash insoluble in diluted hydrochloric acid.

	U. S. P. IX.	German V	Austrian VIII	Helvetian IV	Netherlands IV	Recent literature
Gambir (Catechu) ....	9	6	5	5	5	3.03-32.0
Gentiana .....	6		5	6	2-6	2.5 - 5.42
Glycyrrhiza .....	7		6	6	6	4.4 - 8.96
Granatum .....	16		10	15.5	15	3.63-16.60
Guaiacum .....	4		1	1.5		1.63-11.7
Humulus .....	8					9.70-10.13
Hyoscyamus .....	30	24	20			17.39-31.54
Ipecacuanha .....	1.8-4.5		6	1.8-4	1.8-6	2.83- 9.34
Jalapa .....	6.5	6.5	5	6.5		3.2 - 7.55
Kino .....	3			2		1.47- 5.9
Krameria .....	5		5			1.4 - 4.46
Lactucarium .....	10				10	4.91- 6.9
Linum .....	6	5	5	5		3.3 - 5.85
Lobelia .....	8		8			5.1 -11.65
Lupulinum .....	16		10	10	6	6.60-38.25
Lycopodium .....	3	3	3	3	5	1. - 4.10
Matricaria .....	13		13			12.4 -14.8
Moschus .....	8			8		
Myristica .....	5		3	5		1.23- 3.3
Myrrha .....	8.5	7	6	6	5	4.1 -15.65
Nux Vomica .....	3.5	3		3.5	3	1.25- 3.62
Physostigma .....	7					
Piper .....	2*		5			0.12*- 8.3
Podophyllum .....	3					3.6 - 5.36
Pyrethrum .....	5					4.7 - 7.5
Rhamnus Purshiana ...	8		6		10	4.14- 8.7
Rheum .....	13	12	12	13		7.1 -12.12
Santalum Rubrum .....	3		5			
Sarsaparilla .....	10		8			3.6 -34.57
Sassafras .....	30					27.85-13.38
Scilla .....	8	5	8	5		1.8 - 4.2
Senega .....	5		5			2.6 - 5.7
Senna .....	12	12	10	10	6-8	8.2 -14.32
Senna .....	3*					
Sinapis Alba .....	9		5	5	8	5.2 - 8.06
Spigelia .....	10					7.93-40.81
Stillingia .....	5					5.42- 6.85
Stramonium .....	20	20	20			5.8 -22.16
Strophanthus .....	5		5			3.8 - 4.8
Taraxacum .....	10		8			5.42-14.8
Tragacantha .....	3.5	3.5		3.5	3.5	1.88-29.
Triticum .....	3		3			0.96- 3.31
Uva Ursi .....			4			2.1 - 7.01
Valeriana .....	20		10	12		6.8 -32.73
Vanilla .....	6		10	12		
Zingiber .....	8	7	5	7	8	3.10- 7.9

\* Ash insoluble in diluted hydrochloric acid.



## NOTES ON THE ESTIMATION OF MORPHINE AND ON LLOYD'S REAGENT.<sup>1</sup>

By H. M. GORDIN and J. KAPLAN.

1. Attempt to shake out morphine with a mixture of alcohol and chloroform from a saturated solution of potassium carbonate.

When a saturated solution of potassium carbonate is shaken with alcohol or a mixture of equal volumes of alcohol and chloroform, most of the alcoholic solvent very quickly separates out on the surface of the heavier aqueous layer. This was proved by adding a definite volume of the alcoholic liquid to an equal volume of the saturated solution of potassium carbonate, shaking the mixture vigorously, and reading off the volume of the upper layer after the liquid has separated in two layers. In all cases the volume of the alcoholic layer was only a little less than the volume of the alcoholic liquid originally taken.

Owing to there being no good immiscible solvent for the extraction of morphine from the solution of its salts in water, an attempt was made to saturate such a solution with potassium carbonate and to use a mixture of equal volumes of alcohol and chloroform as immiscible solvent. The aqueous liquid, after being shaken once with an equal volume of the alcoholic liquid, using about 40 c.c. of each for about 0.1 g. of morphine in the form of salt, gave no test, in acidified solution, with Mayer's or Wagner's reagent, while, on the other hand, the alcoholic liquid was found to contain, besides morphine, small amounts of potassium carbonate, together with small amounts of other substances, coming either from impurities in the carbonate, or from a partial decomposition of morphine by the latter, or from both sources. Even when the potassium carbonate was previously washed with alcohol and dried, the alcoholic solution of the morphine contained small amounts of other substances.

It was thought that by washing the residue left after distilling off the alcoholic liquid from the morphine with a saturated solution of the alkaloid the impurities could be eliminated so that the morphine could be determined alkalimetrically. For this purpose definite amounts of morphine were dissolved in acidified water, the solution

<sup>1</sup> Read at the Detroit meeting of the American Pharmaceutical Association, 1914.

saturated with potassium carbonate, either ordinary or previously washed with alcohol, and then shaken with a definite volume of equal volumes of a mixture of alcohol and chloroform. After complete separation of the liquid into two layers, an aliquot portion of the alcoholic layer was drawn off and evaporated to dryness. The residue was washed with a saturated solution of morphine in water until the washings gave no test for potassium carbonate with phenolphthalein, and the morphine determined alkalimetrically, using  $N/25$   $H_2SO_4$  and  $N/50$   $KOH$ . The indicator was methyl-red.

The experiments showed that in all cases the amount of morphine found exceeded the amount originally taken, the variation being from 2 to 15 per cent. Hence the method, at least in the form here described, is not reliable.

## 2. Extraction of alkaloids by means of Lloyd's reagent.

Owing to the facility and completeness of precipitation of alkaloids by Lloyd's reagent, it was thought that this reagent could be advantageously used for the quantitative extraction of alkaloids from their original sources or, in general, from the solution of their salts in water.

It is evident that in order to attain this aim it is necessary to prove that the alkaloids, once precipitated by Lloyd's reagent, can be readily and completely recovered from the precipitate containing alkaloid and reagent. With a view of determining this point, the following experiments were carried out:

A definite amount of morphine was dissolved in an excess of dilute sulfuric acid, the alkaloid completely precipitated with an excess of Lloyd's reagent, and the precipitate washed with water till the washings gave no test for sulfuric acid. The precipitate was dried at  $60^\circ$  and then repeatedly extracted with boiling methyl alcohol, which is a very fair solvent for morphine. The solvent was evaporated to dryness, and the residue weighed. This residue was free of sulfuric acid, showing it to be probably free morphine, but its amount was less than 4 per cent. of the morphine originally taken.

The precipitate was then again extracted with methyl alcohol to which a small amount of ammonia had been added, and the residue left after again evaporating the solvent weighed. The total amount of alkaloid recovered by the two successive extractions was about 90 per cent. of the morphine taken.

Another experiment was made with strychnine, using chloroform, which is an exceptionally good solvent for this alkaloid. A dilute

solution of strychnine in water acidified with sulfuric acid was completely precipitated with an excess of Lloyd's reagent, and the precipitate, after thorough washing with water, dried at 60°. A portion of the precipitate containing about 0.2 g. of strychnine was suspended in a little water containing an excess of ammonia, and then repeatedly shaken out with successive portions of chloroform, using 20 c.c. of the latter for the first shaking and 15 c.c. each time afterwards. It was found that even after ten consecutive operations the chloroform did not remove all of the alkaloid, as was shown by evaporating some of the chloroformic extract to dryness, taking up the residue with acidified water, and testing the resulting solution with Mayer's and Wagner's reagents, both of which continued to give a heavy precipitate. Hence by this method it is extremely difficult quantitatively to recover the strychnine from a solution of its salts in water. Whether other methods would be more successful will have to be determined by further experimentation.

3. Attempt to facilitate the removal of strychnine from the precipitate obtained by adding Lloyd's reagent to a solution of a salt of the alkaloid in water.

The precipitate obtained by adding an excess of Lloyd's reagent to an aqueous solution of a salt of strychnine is almost perfectly tasteless, though it contains all of the alkaloid of the original solution. This seems to suggest the view that the reagent forms with the alkaloid an exceptionally stable combination, and this view is further strengthened by the fact that, as was shown above, it is extremely difficult completely to recover the alkaloid from the precipitate.

On the other hand, as will be reported later by Dr. McGuigan, the precipitate acts physiologically very much like strychnine diluted with an inactive substance, showing that in the living digestive apparatus the union of alkaloid and reagent is readily disrupted. Since it was reasonable to ascribe this disrupting effect to the digestive enzymes of the animal body, experiments were made in order to determine whether some of these enzymes would show the same disrupting effect *in vitro*. If this were so, dilute hydrochloric acid in presence of pepsin, or chloroform in presence of alkali and either ptyalin or trypsin, readily ought to extract the strychnine from the precipitate. The following experiments were, therefore, carried out with these enzymes:

Pepsin.—The thoroughly washed and dried precipitate obtained

by adding an excess of Lloyd's reagent to an aqueous solution of strychnine sulfate was digested with very dilute hydrochloric acid containing a little pepsin, shaking the mixture for an hour and then filtering. The filtrate was tested with Mayer's and Wagner's reagents. Neither of these gave any indication of the presence of an alkaloid. Hence *in vitro* pepsin has no disrupting effect on the precipitate.

Ptyalin and Trypsin.—The precipitate was suspended in a very dilute solution of ammonia containing either ptyalin or trypsin, and the mixture repeatedly shaken out with chloroform. It was found that even after ten successive treatments with chloroform the precipitate still retained some of the strychnine. Hence these enzymes, too, have no disrupting effect on the precipitate.

• NORTHWESTERN UNIVERSITY SCHOOLS OF PHARMACY AND DENTISTRY.

## THE SIXTY-SECOND ANNUAL MEETING OF THE AMERICAN PHARMACEUTICAL ASSOCIATION.

The 1914 meeting of the American Pharmaceutical Association was held in the city of Detroit during the week of August 24–29, 1914, and was, in fact, a joint meeting of that Association with the Michigan State Pharmaceutical Association, the Michigan Pharmaceutical Travelers' Association, the Conference of Pharmaceutical Faculties and the National Association of Boards of Pharmacy. More than 800 persons were registered, and the sessions of the several associations enumerated and also the scientific meetings of the several sections of the American Pharmaceutical Association were very well attended. It was not unusual to have four, and even five, sessions going on at the same time, so that it would be practically impossible for any one person to reflect the proceedings even in part, and in this report nothing more ambitious will be attempted than to try and reflect in outline the happenings of the week as they appealed to an interested participant.

The first general session of the Association was called to order by President George M. Beringer on the afternoon of August 24th. The local committee had very considerably neglected to provide the usual addresses of welcome, so that, contrary to established pre-

cedent, the proceedings were inaugurated by the reading of the President's address.

The address presented this year was an unusually comprehensive communication that touched on many important features of association work and embodied a number of recommendations that should contribute materially to make for real progress in true pharmacy. The address was listened to attentively by all of the members present, and was subsequently referred to a committee of five to report at a later session.

Following the reading of the address of the president, a number of representatives and delegates were requested to present felicitations or reports, and these addresses, with the usual recess for the selection of members of the nominating committee, served to extend the first general session to about the usual late hour for adjourning.

The second general session of the Association was devoted largely to routine business, including the presentation of reports of the various committees. The only item of business regarding which there appeared to be a difference of opinion was the report of the committee on time and place of next meeting, and this was made the special order of business at an extra session held on Friday evening.

Many of the members of the Association are interested only in the work of one or the other of the sections, and these members, at least, had no cause to be dissatisfied.

The programs of the several sections of the Association included a total of more than 125 communications, some of which were of more than usual interest. In the following paragraphs an effort will be made to reflect the nature of the programs themselves rather than attempt to present a comprehensive review of what was said by the individual essayists.

The Section on Scientific Papers, or "Scientific Section," as it was generally designated on the programs for this year, had, as usual, a liberal and varied selection of communications. Edsel A. Rudiman, of Nashville, Tenn., presided, and Wilbur L. Scoville, of Detroit, served as secretary. The printed program contained a total of 42 titles, including discussions on: Radium, biological products, immunology, pharmacodynamic assay methods, the assay of opium, the manufacture of fluidextracts, the nature of the menstruum for official tinctures, the estimation of calomel, the physical properties of volatile oils, the growing of plant drugs, the differentiation of true oil of wintergreen from synthetic methyl salicylate, and many other

subjects equally interesting to the pharmacist who is at all desirous of keeping in touch with the progress that is being made along scientific lines. The papers presented this year, while perhaps not epoch-making, serve to reflect progress in a variety of lines of research.

Three sessions were held and ample time given for the discussion of the several communications that were presented.

At one of the sessions of this section the scope of Hygienic Laboratory Bulletins entitled "Digest of Comments on the Pharmacopœia of the United States of America and on the National Formulary" was discussed and a resolution adopted, the purport of which was that the Digest of Comments be continued along the lines on which it has been developed, and that, if possible, future volumes of the compilation be published more promptly so as to make them increasingly valuable to the workers in scientific pharmacy, who find the publication useful as a reference book on current literature relating to articles included in the Pharmacopœia and the National Formulary.

The officers for the coming year are: Chairman, Herman Engelhardt, Baltimore; secretary, William Mansfield, New York.

The Section on Education and Legislation, under the able direction of Hugh Craig, Chicago, as chairman, and F. H. Freericks, Cincinnati, as secretary, was scheduled for three sessions with a program including some 18 communications. Legislation and the need for enforcing existing laws were discussed at some length. The chairman, in his address, expressed the opinion that legislation is an over-exploited remedy for pharmacaal ills and that education, while slower, is more promising. He also called attention to some of the educational needs of pharmacy, and deplored the lack of efficient pharmacaal educators.

The report of the Committee on National Legislation and of the delegates to the Drug Trade Conference was followed by a rather lively discussion on legislative matters. The section subsequently adopted a resolution endorsing the Harrison anti-narcotic measure in the form in which it passed the Senate, and urged its final adoption into law.

The officers of the section for the coming year are: Chairman, F. R. Freericks, Cincinnati; secretary, R. A. Kuever, Iowa City.

The Section on Practical Pharmacy and Dispensing, under the direction of the chairman, F. W. Nitardy, Denver, and the secretary, Cornelius Osseward, of Seattle, introduced a rather novel feature in the nature of experience meetings that, continued at future meetings,

might well serve to bring about an appreciation of existing conditions in pharmacy and thus make for an unprecedented degree of progress. The program for this section, while it contained but a total of 25 titles, occupied no less than five sessions, two of which were held during the boat ride on Thursday afternoon and evening. The chairman himself presented two exceptionally interesting communications, one on the dispensing of ointments in collapsible tubes, and the second on the preparation of flake agar-agar. For the latter purpose he recommends moistening the substance with water, passing through an ordinary meat-chopper, and then thoroughly drying.

By far the greater amount of time at three of the sessions was devoted to the consideration of a number of pharmaceutical queries. The answers that were offered evidenced the need for developing practical commercialism in pharmacy if pharmacists are to retain any of the business that should be theirs. The material offered, while not particularly reassuring so far as present-day conditions may be concerned, was nevertheless promising, and if repeated, particularly in connection with local branch meetings or in connection with actual demonstrations, would go far toward bringing about necessary reforms in future. The officers for the coming year are: Chairman, Cornelius Osseward, Seattle; associate, D. F. Jones, Watertown, S. D.; secretary, I. A. Becker, Chicago.

The Section on Pharmacopœias and Formularies presented a program containing 12 communications and a general discussion on 400 or more new or modified preparations proposed for the U. S. P. IX and the N. F. IV. The section proceedings were conducted by E. Fullerton Cook, of Philadelphia, and in the absence of the secretary John K. Thum, of Philadelphia, was elected to act as secretary. In accordance with a decision of the Council, this section becomes a sub-section or branch of the Section on Practical Pharmacy and Dispensing, as which the work so successfully inaugurated during the two years of its existence as a distinct section will no doubt be continued.

The Section on Commercial Interests, under the very able management of Harry B. Mason, of Detroit, who had been appointed to serve as chairman in place of Gus Lindvall, resigned, devoted two sessions to the discussion of twenty or more communications. By far the greater number of the papers on the program were matters relating to practical pharmacy, while others had little or nothing to do with pharmacy and were, therefore, not germane to a meeting

that should make for progress in pharmacy as such. The chairman, in his address, properly asserted that the existing "scorn of commercialism in the drug business is the worst kind of stupidity." It is equalled, perhaps, only by that of "the old-school pharmacist" who persists in speaking of the "ethical" pharmacist and of "ethical" pharmacy. In concluding his address the chairman made the prediction that the college or school of pharmacy which now essays to teach its students the science of pharmacy will within the next 50 years to come really teach them how to run a drug store. This prediction involves a degree of progress in pharmacy that many persons would be pleased to see brought about in much less time than the limit set by Mr. Mason. The officers of this section for the coming year are: Chairman, E. H. Thiesing, Cincinnati; secretary, M. Stolz, Syracuse.

• The Historical Section held a well-attended session, at which a number of matters of pharmaceutic interest were discussed. W. C. Alpers, Cleveland, presided, and F. T. Gordon, Philadelphia, served as secretary. Prof. Edward Kremers, in the course of a lecture on "The Study of the History of Pharmacy," demonstrated, by the exhibition of a number of lantern slides, that the subject could be made both interesting and profitable to pharmaceutical students and might well be made an integral part of the pharmaceutical curriculum. The officers of this section for the coming year are: Chairman, F. T. Gordon, Philadelphia; secretary, A. H. Clark, Chicago; historian, E. G. Eberle, Dallas, Texas.

The meetings of the Women's Section were presided over by Mrs. J. G. Godding. A number of interesting papers were read and discussed, and the section is to be continued as heretofore. The officers elected for the coming year are: President, Mrs. John Culley, Ogden, Utah; secretary, Miss Anna J. Bagley, Columbus, Ohio.

The House of Delegates is reported to have had credentials from 261 delegates, representing 100 organizations. Clyde M. Snow, Chicago, presided, and at the concluding session a number of resolutions were adopted and referred to the Council of the Association. The officers for the coming year are: Chairman, W. S. Richardson, Washington; secretary, J. Weinstein, New York.

In addition to the meetings already referred to, the National Association of Boards of Pharmacy and the American Conference of Pharmaceutical Faculties each held a number of sessions, and a joint meeting of these two bodies with the Section on Education and



Legislation of the American Pharmaceutical Association was held on the evening of August 28th.

The Committee of Revision of the United States Pharmacopœia held rather a prolonged conference, at which several highly important matters were discussed. The Committee on National Formulary took advantage of the opportunity to conclude the week by holding several protracted meetings, at which a number of questions in connection with the revision of that book were finally decided, so that the manuscript may now go to the printer.

The final general session, while an unusually long one, will have been well worth the time devoted to it if the changes that were provided for are actually put into operation at future meetings. The amendments to the by-laws that were adopted provide for a material concentration of the work of the sections, including the practical amalgamation of the Section on Pharmacopœias and Formularies with the Section on Practical Pharmacy and Dispensing. The work of other sections is also more clearly outlined and will obviate any agitation for additional sections in the near future.

The report of the Committee on President's Address aroused considerable discussion, and some of the recommendations made by the committee were not approved of. The report of the same committee on the recommendations made by the former secretary of the Association, Prof. Jas. H. Beal, was, on motion, referred to the Council with power to act.

Among the resolutions approved by the Association at this final session were:

A resolution to draft a bill designed to reform the present patent law so as to compel the manufacture in this country of all medicinal products protected by patent;

A resolution endorsing the proposition that graduates in pharmacy only be appointed as members of Boards of Pharmacy;

A resolution endorsing the proposed Congress of National Drug and Pharmaceutical Associations, the object of this resolution being to bring about some form of correlation in the work of the several organizations;

A resolution endorsing bills now pending to bring about standardization of prices on proprietary medicines;

A resolution objecting to the imposition of a stamp tax on proprietary medicine;

A resolution designed to develop the production of botanical drugs in the United States; and

A resolution commending the present scope of the Hygienic Laboratory Bulletins embodying a Digest of Comments on the Pharmacopœia of the United States of America and on the National Formulary, and asking that, if practicable, these bulletins be published more promptly.

Following the usual vote of thanks to the local committees; and a special vote for the local secretary, the officers for the ensuing year were installed and the 62nd annual meeting of the American Pharmaceutical Association was declared adjourned.

Any account of this meeting without some reference to the elaborately planned and carefully carried out social features would be incomplete at best. The local secretary and his efficient assistants had for the nonce devised a program in which the social features did not conflict with the business meetings of the Association or any of its sections, and, despite the very liberal duplication of section sessions during the day, the evenings were free to all but Council members and delegates, to enjoy as they saw fit.

The program as arranged served not alone to provide large and interested audiences at all of the sessions of the Association, but also insured ample time to permit members of the Association to take part in the several outings and informal gatherings that had been provided.

The supper and smoker on Wednesday evening and the river excursion on Thursday afternoon were attended by upwards of 1000 members and friends, and will long be remembered as being among the most unique of the functions held in connection with meetings of the American Pharmaceutical Association.

The graduates of the Philadelphia College of Pharmacy present at the meeting were entertained at luncheon on Wednesday at noon by Frank G. Ryan, a graduate and for some years one of the assistant professors of the college. A total of 53 graduates, representing 21 States, was present, and the occasion offered an unusual opportunity to make and to renew acquaintances among graduates of the college.

The officers of the American Pharmaceutical Association for the coming year are: Honorary president, G. H. Schaefer, Fort Madison, Iowa; president, Caswell A. Mayo, New York; vice-presidents, L. D. Havenhill, Lawrence, Kan., C. H. Packard, Boston, Mass., Chas. Gietner, St. Louis, Mo.; permanent secretary, W. B. Day,

Chicago, Ill.; treasurer, H. M. Whelpley, St Louis, Mo.; reporter on the progress of pharmacy, C. Lewis Diehl, Louisville, Ky.

The nominees to be voted for by mail are:

For president: W. C. Alpers, Cleveland; W. J. Teeters, Iowa City, Iowa; L. D. Havenhill, Lawrence, Kan.

For first vice-president: C. H. LaWall, Philadelphia; L. A. Seltzer, Detroit; D. F. Jones, Watertown, S. D.

For second vice-president: E. H. Ruddiman, Nashville, Tenn.; E. O. Kagy, Des Moines, Iowa; F. W. Nitardy, Denver, Col.

For third vice-president: L. A. Brown, Lexington, Ky.; E. N. Gathercoal, Chicago, Ill.; Cornelius Osseward, Seattle, Wash.

For member of Council: F. M. Apple, Philadelphia; Philip Asher, New Orleans; E. C. Bent, Dell Rapids, S. D.; H. V. Army, New York; Charles B. Jordan, Lafayette, Ind.; R. H. Walker, Gonzales, Tex.; J. O. Burge, Nashville, Tenn.; Andrew Scherer, Chicago; Caswell A. Mayo, New York.

The 1915 meeting of the Association is to be held in San Francisco, Cal., at a time to be fixed by the Council.

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## THE IDENTIFICATION OF ARTIFICIAL SILKS ESPECIALLY PREPARED FOR THE PRACTICAL MILL MAN AND DYER.<sup>1</sup>

By LOUIS J. MATOS, PH.D.

Owing to the constantly increasing use of artificial silks and the consequent confusion arising in dye-houses and silk mills generally, due to the occasional, though unintentional, mixing of lots, it becomes a matter of some importance for the dyer or manager to be able to identify with certainty the several important kinds of artificial silks on the market.

Where a dyer goes on from day to day with his work, and on one kind of silk, it is a matter of some consequence when he finds himself confronted with the problem of dyeing a new lot of different kind of silk that does not come out as expected, or which seems to offer difficulties during the dyeing.

Many instances are familiar to dyers where lots of mixed artificial silk have been sent to the dye-house, and inequality in the dyeing was

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<sup>1</sup> Reprinted from *The American Silk Journal*; *Dyestuffs*, Dec., 1913, No. 12.

not discovered until near the end of the operation, when it became a matter of great skill to bring up the shade of the indifferent skeins to the shade of the main lot. This condition could have been anticipated had the dyer been acquainted with the fact that the entire lot of silk was not of one kind.

From time to time there have been published tests and reactions with chemicals to be used in distinguishing the several kinds of artificial silks, but the practical application of which, in the dye-house or office, seems to offer some obstacles in the hands of those not actually acquainted with the details of making reactions. It seems that while the method of making the tests is simple enough, the greatest difficulty is in having the solutions or reagents properly compounded and in conducting the tests afterwards.

Simple descriptions alone do not seem to meet the case entirely. Of course, there is nothing to take the place of a practical demonstration of a testing method when carried out by one who is practically familiar with the proper sequence of the operations.

On the other hand, many of the methods for fibre testing that have been published, while apparently intended for dyers and practical mill men, being those most concerned, are, as a rule, written for the chemist with some experience, as only such could possibly have the unusual reagents and apparatus, or even the apparently delicate manipulative skill, to handle both satisfactorily.

Without question, the most satisfactory means to identify artificial silk is to make use of the microscope, but as very few mills are equipped with this valuable instrument, and fewer still are proficient in making use of it, we will omit its discussion as applied to artificial silk and confine ourselves exclusively to the chemical or *wet methods* that experience has taught us as being the most satisfactory.

To identify artificial silk properly requires that the person attempting the work should have at hand a small set of chemical reagent bottles of not more than two-ounce capacity and with glass stoppers. Such bottles are not costly and may be obtained through a local druggist; the style known as "XX Tinctures" are admirably suited for the purpose. They are to be filled with the following reagents, which can be procured from a chemical supply house or prepared by a friendly pharmacist or chemical friend.

The following constitutes the list and the methods for their preparation:

No. 1. *Glycerinated Sulphuric Acid.*

Pure Glycerin ..... 10 c.c.

Distilled Water ..... 5 c.c.

Add slowly with constant stirring, a few drops at a time, Pure Concentrated Sulphuric Acid ..... 15 c.c.

No. 2. *Iodo-iodide of Potassium.*

Distilled Water ..... 30 c.c.

Potassium Iodide ..... 0.3 gr.

Iodine, an excess.

No. 3. *Chlor-iodide of Zinc.*

Distilled Water ..... 30 c.c.

Fused Chloride of Zinc ..... 1.75 gr.

Filter and add to clear filtrate Iodine to saturation.

No. 4. *Cold Concentrated Sulphuric Acid.*

No. 5. *Half Saturated Chromic Acid.*

No. 6. *A 40 per cent. Caustic Potash Solution.*

No. 7. *Copper-Oxide-Ammonia.*

This is an important reagent in all fibre work. It should be made with great care by preparing a solution of copper oxide in ammonia to saturation, and passing through it a current of air freed from carbon dioxide, by first being passed through a solution of caustic potash.

No. 8. *Nickel Oxide Ammonia.*

Nickel Sulphate in crystals ..... 2 gr.

Water ..... 30 c.c.

Precipitate the nickel with caustic soda and filter; then dissolve the precipitate in a mixture of:

Concentrated Ammonia ..... 8 c.c.

Water ..... 8 c.c.

No. 9. *Alkaline Copper Glycerin Solution.*

Sulphate of Copper ..... 3 gr.

Water ..... 30 c.c.

Glycerin ..... 1.75 gr.

to which is added a sufficient quantity of caustic potash solution to precipitate the copper and redissolve it.

No. 10. *Diphenylamine-Sulphuric Acid Solution.*

Diphenylamine ..... 1.57 gr.

Concentrated Sulphuric Acid ..... 25 c.c.

The operator should keep these bottles in a closet when not in use and at all times free from dust. The label, besides the name, should also have the formula written upon it.

The apparatus required to make the tests consists of a dozen small plain white butter dishes, a dozen small test-tubes of short length and not over half an inch in diameter, and a spirit lamp or Bunsen burner to supply heat. There should also be at hand two small bottles or tubes containing red and blue litmus paper. The entire outfit is procurable under five dollars.

There are five kinds of artificial silk generally met with in commerce, as follows:

Collodium Silk (Strictly nitro silks).

Cellulose Silks.

Viscose Silks.

Acetate Silks.

Gelatin Silks.

The first important test to make is to determine whether the silk under examination is made from gelatin or not.

Take one of the test-tubes, see that it is clean and dry inside, and place at the bottom of it a small tuft of the silk about the size of a small pea when rolled between the fingers. In the open end of the tube insert a piece of red litmus paper, bending the end over so that the strip will not slide down the tube.

With a handle made of several folds of paper around the neck of the tube so as to permit one to hold it comfortably, place the closed end of the tube in the flame of the Bunsen burner or spirit lamp, giving the tube a slight to and fro motion until the fibres in the tube begin to char and vapors are seen to arise. When these vapors are observed to come out of the open end of the test-tube, note whether the color of the red litmus paper changes to blue. If such a change takes place it is due to the presence of ammonia gas resulting from the charring of the fibres and which could only come from gelatin silk. These vapors may also have the odor of burning horn or hair, which odor is further indicative of the presence of gelatin.

On the other hand, if the litmus paper does not change color, acid fumes may be present and are to be confirmed by repeating the test, but using *blue* litmus paper, and upon it turning red, indicates that the silk may be any one of the four above-named makes.

To distinguish finally between the several artificial silks emitting acid fumes with heat, place two of the butter dishes side by side; in one, place some of the silk fibre and upon it pour some of reagent No. 1, and let soak for a few minutes, and then afterwards add a

few drops of reagent No. 2. In the second dish put some of the fibre and a small amount of reagent No. 3, and note carefully what changes in color, if any, take place. If both samples show a distinct yellow coloration, the silk is *Acetate Silk*.

On the other hand, if the coloration is blue, the silk may be either *collodium*, *cellulose* or *viscose silk*, which is confirmed if the coloration shown in the second dish is reddish-violet. To differentiate between these three silks just mentioned, place a small tuft of the fibres in a dry dish and pour upon it a small amount of cold concentrated sulphuric acid (No. 4). If the silk dissolves rapidly, the specimen is either collodium or viscose silk; cellulose silk, *i.e.*, Pauly, Fremery, etc., dissolves slowly.

Confirmatory tests are made in test-tubes with the chromic acid solution (No. 5) in the cold, when these three silks dissolve gradually, and upon the tube being heated, dissolve quickly. When treated in the same manner with warm caustic potash solution (No. 6) these three silks, together with the acetate silk show a distinct swelling, while *gelatin silk* dissolves rapidly and completely.

The copper oxide ammonia test (No. 7) when applied in a test-tube first causes a swelling and dissolves collodium and viscose silks, but acetate silk swells without dissolving, and gelatin silk takes a bluish-violet coloration without dissolving.

The nickel-oxide-ammonia reagent (No. 8), when applied both cold and warm to a sample of artificial silk in the test-tube, causes a swelling of the fibres but without dissolving them. This applies to collodium, cellulose, viscose, and acetate silk, but not to gelatin silk, which latter takes a brown coloration without dissolving.

The alkaline-copper-glycerin solution (No. 9) has no action even after long boiling upon the first four silks above mentioned, but gelatin silk dissolves after a short time.

A convenient reagent for artificial silk is the concentrated sulphuric acid-diphenylamine solution (No. 10) which has been extolled as the one reagent for this class of work, but as a matter of fact its usefulness is limited exclusively to differentiate only the nitro silks from the others. With nitro silks of the Chardonnet type, it causes a distinct blue coloration, while the other silks remain uncolored. This diphenylamine reaction lasts but a comparatively short time, reaching its maximum intensity within five minutes after adding the reagent, when it gradually disappears.

In order to be in the position where one can absolutely and

certainly pass judgment upon the identity of a given silk sample, the operator should have at hand a collection of true type samples obtained directly from the artificial silk manufacturers and to make the above outlined reactions repeatedly, systematically and with care. By care is meant not being too hasty in forming a conclusion, and to disregard and reject completely any test that one may have made, into which the element of doubt enters.

With such a set of proved samples at hand and a set of reagents as above outlined, when unusual lots are received by the dye-house, or where silk is received from unfamiliar sources, its identity can be accurately determined.

The foregoing details refer to undyed artificial silk, but to identify dyed silk by chemical means requires that it should be stripped of its color, which is generally very easily accomplished by means of Hyraldite or some other equally efficient stripping agent.

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## BOOK REVIEWS.

THE ART OF COMPOUNDING. A Text-Book for Students and A Reference Book for Pharmacists at the Prescription Counter. By Wilbur L. Scoville, Ph. G., formerly Professor of Theory and Practice of Pharmacy in the Massachusetts College of Pharmacy; member of the Eighth Committee on Revision of the United States Pharmacopœia and of the Second and Third Committees of the Revision of the National Formulary. Fourth edition, revised and enlarged, with 76 illustrations. Philadelphia: P. Blakiston's Son & Co., 1012 Walnut Street. \$3 net.

This excellent volume, prepared by the author when he was a professor in the Massachusetts College of Pharmacy, has become one of the most popular books on the prescription and its compounding that we have. That it has run through four editions shows that both the publisher and author are alive to the progress that is being made in pharmacy and the development of this subject in particular. Among the innovations in the present volume may be mentioned the inclusion of illustrations. These are numerous, and not only include the implements for preparing small quantities of remedies, as in general prescription work, but also the forms and apparatus in use by manufacturers. The author's wide experience in all phases of the



drug business makes him unusually well qualified to handle manufacturing processes in a practical way.

For the purpose of adding interest to the study of individual prescriptions, some 225 prescriptions from State Board examinations have been added in a systematic way. This compilation will be found to be of great value to the apprentice in his study of the methods of mixing and conditions suitable for their compounding. A valuable chapter on biological products has been added and will prove of great interest to pharmacists. The new developments in the pharmaceutical applications of sterilization are noted in several portions of the book.

THE ELECTRICAL CONDUCTIVITY AND IONIZATION CONSTANTS OF ORGANIC COMPOUNDS. A bibliography of the periodical literature from 1889 to 1910 inclusive, including all important work before 1889 and corrected to the beginning of 1913. Giving numerical data for the ionization constants at all temperatures at which they have been measured; and some numerical data of the electrical conductivity. By Heyward Scudder. New York: D. Van Nostrand Company, 25 Park Place. 1914. \$3 net.

This is a very valuable compilation, containing all of the valuable data on the electrical conductivity and ionization of organic compounds, practically everything of value being included, with very few exceptions. The references to subjects of biological interest, as albumin, blood, sap, etc., are complete only for the last few years (roughly, the last five or ten), but afford a means both of knowing where to get at the important work, which is all recent, and where to start in any more thorough search of the literature. Neither are the references to the resistance of substances such as rubber, wood, etc., given, as they are of value chiefly in connection with the question of electrical insulation, although they have some biological interest. References to the conductivity of inorganic compounds in organic solvents have not been looked up specially, though in cases where salt formation is to be expected they have been taken. In addition, a number of references are given on the conductivity of molten salts as well as certain inorganic compounds. In the tables a number of references are given to the work on the comparative strength of different compounds (measured in various ways), because to many chemists the chief value of the ionization constant of a compound, or of a measurement of its electrical conductivity, is to determine its strength as an acid or a base.

The book is divided into a set of tables arranged according to the names of the compounds, containing all the data that may be given, with a bibliography of all the references to each compound; a formula index to the compounds; a bibliography arranged according to the names of authors; a subject index to certain subjects; and a journal list giving the names of all journals examined, with the number and date of the last volume examined.

CHEMICAL REAGENTS. Their Purity and Tests. Authorized translation of " *Prüfung der Chemischen Reagenzien auf Reinheit* " (Zweite Auflage) von E. Merck. By Henry Schenck, Second edition. New York: D. Van Nostrand Company, 25 Park Place. 1914. \$1 net.

This translation in method of treatment, closely resembles that of the German work. It includes, however, numerous articles which have come into prominence since the earlier work was published. Among the subjects included for the first time in this edition the following may be mentioned: Alphanaphthylamine, Ammonium Chromate, Ammonium Molybdate Solution, Ammonium Persulphate, Benzidine for Blood Test, Bismuth and Potassium Iodide Solution, Carbon Tetrachloride, Carmin-Fibrin, Chromium Trioxide for Carbon Determination, Cobalt Nitrate (Free from Nickel), Cobalt Oxide, Copper Hydroxide, Copper Oxide-Asbestos, Devarda's Metal, Dicyandiamidine Sulphate, Dimethylglyoxime, Dimethylparaphenylenediamine Hydrochloride, Ferric Oxide, Glass Wool, Hydrazine Sulphate, Indigo Carmin, Indigo Solutions, Lead Peroxide, Granulated Magnesia Mixture, Magnesite, Manganese Metaphosphate Solution, Methyl Red, Platinized Pumice Stone, Poirrier's Blue C<sub>4</sub>B, Potassium Persulphate, Quartz Sand, Sea Sand, Silver-Asbestos, Sodium-Cobaltic Nitrate Solution, Tetramethylparaphenylenediamine Hydrochloride, Yellow Oxide of Mercury.

A number of changes have been made, some of these having materially raised the standard of purity. Coincident with this improvement is the inclusion among the references of important new contributions upon the uses and methods of testing reagent chemicals. The tables of equivalents of standard solutions have been replaced, in response to a suggestion, by a table giving approximate strengths and brief directions for the preparation of solutions for reagent purposes, compiled from published writings. Another valuable feature in this translation is the parenthetical statement appended to each

test, giving in terms of percentage the minimum amount of the impurity which would be recognized by the test. This work will be found of very great value to analysts in the examination of reagents.

A CRITICAL REVISION OF THE GENUS EUCALYPTUS. By J. H. Maiden, Government Botanist of New South Wales and Director of the Botanic Gardens, Sydney. Parts XVIII to XXI. Published by authority of the Government of the State of New South Wales. Sydney: William Applegate Gullick, Government Printer. 1913.

These valuable monographs by Mr. Maiden continue to be of very great interest. In the most recent pamphlets the following species are critically considered: *Eucalyptus macrocarpa*, Hook, *Eucalyptus Preissiana*, Schauer, *Eucalyptus megacarpa*, F. v. M., *Eucalyptus globulus*, Labillardiere, *Eucalyptus Maidenii*, F. v. M., *Eucalyptus urnigera*, Hook f., *Eucalyptus goniocalyx*, F. v. M., *Eucalyptus nitens*, n. s. d., *Eucalyptus elcophora*, F. v. M., *Eucalyptus cordata*, Labill., *Eucalyptus angustissima*, F. v. M., *Eucalyptus gigantea*, Hook, *Eucalyptus longifolia*, Link and Otto, *Eucalyptus diversicolor*, F. v. M., *Eucalyptus Guilfoylei*, Maiden, *Eucalyptus patens*, Benth, *Eucalyptus Todtiana*, F. v. M., *Eucalyptus micranthera*, F. v. M., *Eucalyptus cinera*, F. v. M., *Eucalyptus pulverulenta*, Sims, *Eucalyptus cosmophylla*, F. v. M., *Eucalyptus gomphocephala*, A. P. DC.

ANNALES DU MUSEE COLONIAL DE MARSEILLE fondees en 1893 par M. Le Professeur Dr. Edouard Heckel et publies sous sa direction. Vingt-et-unieme anne. 3<sup>e</sup> series 1<sup>er</sup> volume (1913). Marseille Musee colonial 5, Rue Noailles, 5 1913.

This volume contains the following monographs: Palms of Madagascar, by MM. H. Jumelle and H. Perrier; Botanical Study of Caysen, an Oleaginous Seed of Sapotaceæ, by Narcel Dubard; Contributions to the Anatomy of the Dypsideæ Palms of Madagascar, by M. J. Achilli; The Orchidaceæ of Madagascar, by M. R. Schlechter; The Cultivated Plants of Central Africa, by M. A. Baudon; A Melastomaceous Plant *Osbeckiees malgaches*, by H. Jumelle and H. Perrier; Analysis of a Tabachir of Indo-China, by E. Laborde.

A large number of very excellent drawings and photographs accompany this volume, and the researches are of very high class. The first volume of the Colonial Museum of Marseilles was published in 1893, so that for more than twenty years the studies on products of the French colonies have been published, reflecting very great credit upon the director, Professor Heckel.

## OBITUARIES.

DAVID H. ROSS.

David H. Ross, of the class of '78, died at his residence and place of business, Almond and Norris Streets, Philadelphia, after a brief illness due to pneumonia. At the time of his death he was 69 years of age and had conducted a retail drug business at his home address for nearly thirty years. Mr. Ross was born in Ireland of Scotch parentage, and came to Philadelphia in his youth. His experience in the drug business was acquired with the firm of Bullock and Crenshaw, for whom he worked as a drug clerk, and, after his graduation, as a salesman. Nearly all his life the deceased was active in pharmaceutical affairs, and held many positions of honor and trust.

He was president of the Alumni P. C. P. in 1893; and for many years was secretary-treasurer of the Philadelphia Wholesale Drug Company. The Philadelphia Association of Retail Druggists, of which he was an active member, also made use of the services of Mr. Ross on many occasions. He was also made treasurer of the Druggists' Building and Loan Association when it was organized a short time ago. He was active in the management of the First Presbyterian Church of Kensington, of which he was an elder. In addition to his other activities, he for many years took a practical interest in political matters and served on the Executive Committee of the Washington party, and was elected to Councils upon the Reform party ticket. He also served as a school director in his home ward for a number of years.

Personally Mr. Ross was aggressive and active in everything he took in hand, and was unusually outspoken and frank in attacking what he considered wrong; and was just as quick to defend what he considered to be right, in the same characteristic manner. Behind the aggressive man of action there was, however, a true man in the broader human sense who endeared himself by strong ties to those who learned to know him well.

W. L. CLIFFE.

PETER P. FOX.

Peter P. Fox, of the class of 1858 of the Philadelphia College of Pharmacy, died on April 24, 1914. He was one of the oldest graduates of the College, and had been a member since 1872. Mr. Fox was born in Leimbach, near Audenaw, Germany, in 1835. He was a Brother of Prof. John Fox, M.D., who graduated from the University

of Bonn, Germany, and was prominently known before the Civil War as a teacher of languages to the children of many of our conspicuous families of those days in Philadelphia. In the War of the Rebellion he enlisted in the 99th Pennsylvania Volunteer Infantry, and served for two years and eight months. At the expiration of his service he came to Philadelphia and started a drug store at Seventy-third Street and Woodland Avenue, West Philadelphia, where he continued the business until his death. Mr. Fox was allied with the American Pharmaceutical Association, the Philadelphia Association of Retail Druggists, and various other bodies. The funeral of Mr. Fox took place on Monday, April 27th, with a Solemn Requiem Mass at St. Clement's Church, Paschalville, of which he was a devout communicant for many years. The remains were laid at rest in New Cathedral Cemetery.

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### CURRENT LITERATURE.

GASEOUS IMPURITIES IN THE AIR OF RAILWAY TUNNELS.—Seidell and Meserve, in *Hygienic Laboratory Bulletin No. 92*, have taken up the question of the composition of the air in railway tunnels, and summarize their work as follows:

(a) On account of the particular conditions in hand, methods for the determination of sulphur dioxide based upon the aspiration of the sample through a small volume of liquid followed by a gravimetric or volumetric determination of the retained sulphur dioxide could not be used. The several possible variations of the iodometric titration were examined and the general source of the errors discussed. It was finally shown that a method of direct titration with  $N/1000$  iodine solution gave, after applying proper correction factors, results of satisfactory accuracy.

(b) Experiments upon the rate of loss of sulphur dioxide on standing showed that in the presence of moisture only a small fraction of the used sulphur dioxide was recovered after one hour. In dry bottles there is usually an inconsiderable loss within the first two hours, although with very dilute mixtures an appreciable loss may occur after one-fourth to one-half hour.

(c) Of quite small amounts of sulphur dioxide liberated in a closed room only about 30 to 60 per cent. could be recovered, depending upon the amount of stirring and the moisture content of the air.

(d) In adapting the iodine pentoxide method to the determination of carbon monoxide in the samples of tunnel air, manipulative improvements involving the use of a new form of absorption bulb and

of a closed aspiration system were developed. The time for a determination was decreased to about one-fourth and the attention which the apparatus required during the passage of the sample through it was reduced to a minimum.

(e) Analyses of mixtures of very small amounts of carbon monoxide with air showed that from 88 to 98 per cent. of the amount present was recovered by the method. On account of the very small actual amounts under consideration, these losses are considered negligible.

(f) The results of the analyses of 88 samples of air from the two tunnels show that on an average there is approximately five times as much of each of the two gases in the Fulton as in the electrified tunnel. In the case of the Fulton Tunnel, the highest amounts were 15.1 parts of sulphur dioxide per million and 267 parts of carbon monoxide per million. The corresponding figures for the electrified tunnel were, respectively, 2.9 parts and 25 parts.

(g) A review of the available literature upon the physiological effects of small amounts of carbon monoxide and sulphur dioxide showed that the concentrations of these gases which produced an unmistakable harmful effect upon man were somewhat greater than the maximum amounts which were found in any of the tunnel-air samples.

KIESELGUHR INDUSTRY.—P. A. Borck in an article (*Metall. and Chem. Engin.*, xii, 109).—This article treats of the properties of kieselguhr, its occurrence at Lompoc, California, and other places, and its treatment. Natural blocks can be obtained by sawing the material; these blocks are fairly strong, have high insulating value, stand heat and cold well, except as to a slight shrinkage, and melt at 1610° C. Light-weight kieselguhr bricks are produced by properly burning the material; they insulate well up to red-heat, but shrink at high temperatures, and must be protected against sudden changes of temperature. They are recommended as backing for more refractory bricks.—*Jour. Franklin Ins.*, 1914, p. 382.

SUPPLY OF POLLANTIN AFFECTED BY WAR.—*Fritzsche Brothers*, New York, advise that their stock of Pollantin Liquid (Dunbar's serum in hay fever) is exhausted; and that, due to the lamentable war conditions, they are unable to replenish in time for the current season's demand.

Also, that but a very limited supply of the Pollantin Powder and Ointment is available.

# THE AMERICAN JOURNAL OF PHARMACY

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NOVEMBER, 1914

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## THE GERMINATION OF BELLADONNA SEED.\*

By A. F. SIEVERS, Chemical Biologist, Office of Drug-Plant and Poisonous-Plant Investigations, Bureau of Plant Industry, U. S. Department of Agriculture.

Since commercial cultivation of belladonna has become a question of practical possibility, the methods of cultivation are receiving more and more attention. Repeated attempts at field sowing have demonstrated quite thoroughly that such methods are not successful. The tenderness and slow growth of the young plants make it a difficult matter to secure a proper stand by that method, even if the seed germinate well and seasonal conditions are favorable. Loss by insects and suffocation by weeds are the principal obstacles encountered after the plants have made their appearance. One of the main difficulties, however, lies in the fact that belladonna seed germinates very slowly and irregularly, and, as a rule, not much over 50 per cent. germinates at all.

During the course of several years many belladonna plants have been propagated by the writer in the greenhouses with very good success. With proper care and the elimination of such disturbing factors as have already been mentioned, the plants grow rapidly and uniformly. It was these experiments that afforded an opportunity of studying carefully the behavior of belladonna seed and its relative vitality. Lack of uniformity in germination and the relatively large percentage of inert seed were noted repeatedly. It was decided, therefore, to undertake some systematic examination of the seed with a view to establishing what types of seed as regards size, weight, and color, and what methods of handling are the most desirable.

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## METHODS OF STUDY.

In the experiments which were conducted in the greenhouse, the seeds were planted in pots of convenient size containing good loose soil. The surface was marked off in rows about three-quarters of an inch apart, and the same number of seeds were placed in each pot for each experiment. The seeds were planted about a quarter of an inch deep, and a thin layer of sand was scattered over the surface. Suitable conditions of moisture and temperature were constantly maintained.

## EFFECTS OF FREEZING ON THE GERMINATION.

Experience has shown that seed sown late in fall usually germinates quickly in spring, while spring-sown seed is much slower in germinating. This fact pointed to the possibility that frost might have a favorable effect in hastening germination. As a definite test a small lot of seed was divided into two parts, one to serve as a check and the other half to be frozen. The freezing was accomplished by placing the seeds in a test-tube with sufficient water to cause them to cling together, and then subjecting the tube to a temperature of  $-12^{\circ}$  C. for five hours. Forty-eight seeds from this frozen lot were sown in one side of a 10-inch pot, while the same number of seeds from the untreated lot were sown in the other half as a check. These seeds were sown on April 13th. The following table gives the number and per cent. germinated at various intervals:

TABLE I.

*Germination of Frozen and Unfrozen Seeds Sown on April 13th.*

Description	Germination							
	Number					Per cent.		
	May 8	May 15	May 22	May 29	May 8	May 15	May 22	May 29
Frozen.....	22	24	25	26	46	50	52	54.2
Check (unfrozen).....	5	10	12	13	10.4	20.8	27	29.2

Figure 1 shows graphically the percentage of total germination at each observation. The effect of freezing is immediately apparent, and the possibility suggests itself of hastening the germination of the seeds in greenhouse work by subjecting them either to cold weather or some such treatment as described above. It also empha-



sizes the value of fall sowing in case direct field sowing is resorted to. It is probable that the influence of the low temperature is largely to accelerate germination rather than to induce seeds to germinate

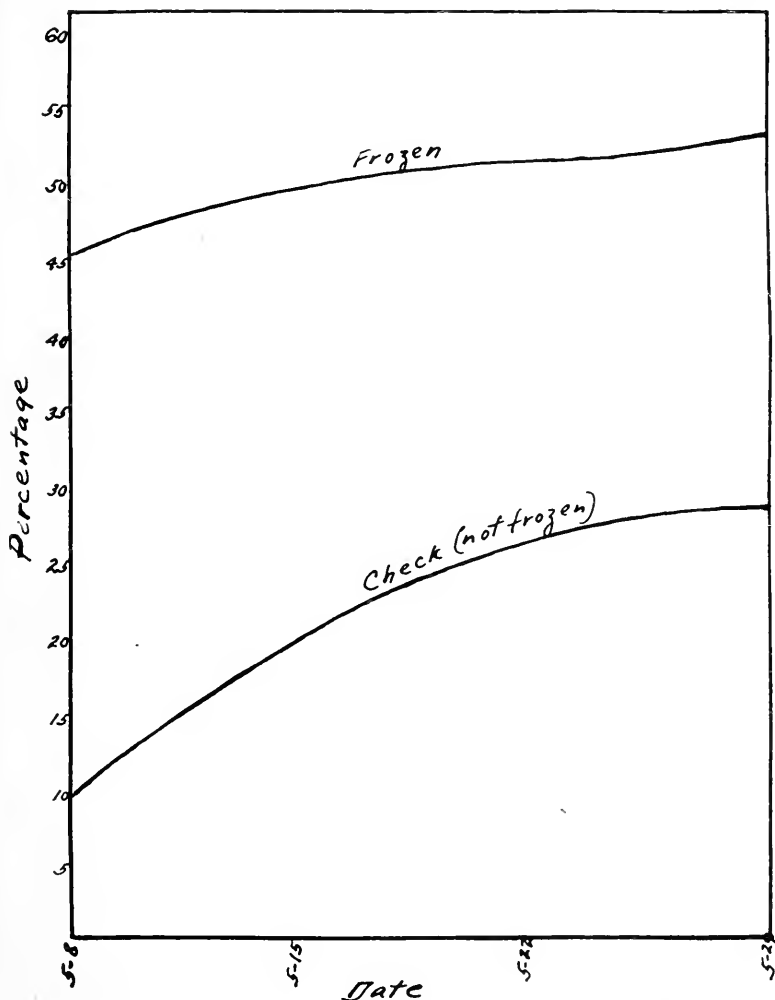


FIG. 1.—Percentage of germination of frozen and unfrozen seed sown on April 13th.

which would not otherwise do so. If this experiment had been carried sufficiently far it would very likely have been found that the check lot would eventually show a percentage of germination not much less than that of the frozen lot.

## RELATION OF SIZE OF THE SEED TO ITS GERMINATION.

Considerable variation in size exists among belladonna seed. The average seed is about one and a quarter millimetre in diameter, while the extremes range from less than one to almost two millimetres. In order to determine the relative weight of these small and large seeds, 500 of both the largest and smallest seeds were separated and weighed in portions of 100 each. Table II shows the results.

TABLE II.  
*Relative Weight of Large and Small Seeds.*

Description	Weight (Gms.)	
	Large	Small
First 100.....	0.1290	0.0897
Second 100.....	0.1276	0.0820
Third 100.....	0.1324	0.0847
Fourth 100.....	0.1350	0.0825
Fifth 100.....	0.1382	0.0906
Total.....	0.6622	0.4295
Average for 100.	0.1324	0.0859

To determine the relative germination of these seeds, 300 of each were sown in two rectangular boxes on April 5th. Each box was divided into 20 rows, with 15 seeds in each row. Figure 2 shows graphically the resulting germination. Table III shows the progress of germination from time to time.

TABLE III.  
*Comparative Germination of Large and Small Seeds Sown April 5th.*

Description	Germination							
	Number				Per cent.			
	May 1	May 8	May 15	May 22	May 1	May 8	May 15	May 22
Large.....	42	131	133	134	14	43.6	44.3	44.6
Small.....	43	145	150	153	14.3	48.3	50	51

From the tables and figures it is at once evident that there is practically no difference in germination due to size. In this particular case the advantage even lies with the small seeds, though the

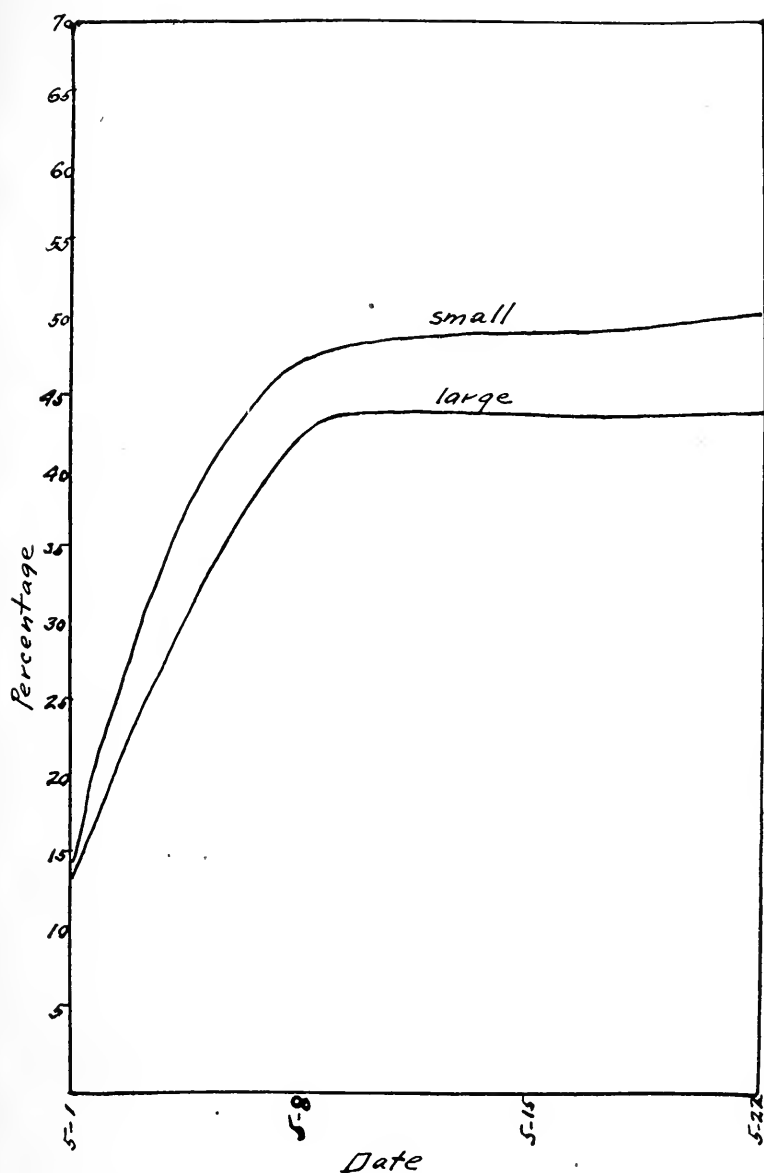


FIG. 2.—Curves showing comparative germination of large and small seed sown on April 1st.

margin is so small that it can hardly be taken to indicate that such is always the case. It appears, then, that the small seeds are in no wise inferior to the larger ones in so far, at least, as concerns the germination. What the relative growth and development of these plants will be is an entirely different problem. There was little to choose between them seven weeks after sowing. However, any inferiority due to seed would very likely not become evident until later in the plant's development. A careful study is being made of this phase of the problem with special reference to the relation of the size of the seed to the development of alkaloids in the plants grown therefrom. It is interesting to note that the progress of the germination is very similar in the two kinds of seeds, as Figure 2 plainly shows.

#### RELATION OF WEIGHT OF SEED TO GERMINATION.

While the size of the seed was found to have nothing to do with the germinating power, the question of the weight of the seed promised to be of greater importance. Like most other seeds, a considerable percentage of belladonna seed is much lighter than the average. It is a question of specific gravity, there being no relationship as to size. In order to determine the percentage of the seed, which is generally found to be inferior as to weight, a method of separating the light from the heavy, based on the specific gravity of the seed, was used, which was briefly as follows: 10 Gms. of seeds previously cleaned from husks and all inert matter are thrown into a tall, lipped beaker of 1 litre capacity and half full of water. After thorough stirring to enable all the seeds to become wet, the water is brought to a stop and the heavy seeds allowed to settle on the bottom, while the light ones remain on or near the surface. The latter are then carefully decanted into a Gooch crucible (the perforations in such a crucible are just small enough to prevent the seeds from going through) attached to a vacuum flask. With a strong current of air pulling through the crucible and occasional stirring the seeds are soon dry and can then be weighed. The heavy seeds are filtered off and dried in a similar way. According to this method, six 10-gramme portions from one general lot of seeds were separated into the light and heavy portions to determine the accuracy of the method. The volume of each portion was determined by placing the seeds in a

tall and very narrow graduated cylinder containing about 1 Cc. to the inch, and the scale divided into tenths. Table IV summarizes the result.

TABLE IV.  
*Relative Per Cent. of Light and Heavy Seed in a General Lot Formed by Separation According to Specific Gravity.*

Portion	Light				Heavy			
	Weight		Volume		Weight		Volume	
	Gms.	Per cent.	Cc.	Per cent.	Gms.	Per cent.	Cc.	Per cent.
1	8.25	82.5	16.1	84.3	1.75	17.5	3.0	15.7
2	7.81	78.1	15.5	81.6	2.19	21.9	3.5	18.4
3	8.12	81.2	16.1	84.7	1.88	18.8	2.9	15.3
4	8.53	85.3	17.2	88.2	1.47	14.7	2.3	11.8
5	8.68	86.8	17.4	88.4	1.32	13.2	2.3	11.6
6	8.05	80.5	15.8	82.3	1.95	19.5	3.4	17.7
Average	8.24	82.4	16.35	84.9	1.76	17.6	2.9	15.1

The results show that the method of separation is fairly accurate within certain limits. Seeds from five individual plants were then separated according to the method just described, with the results as shown in Table V.

TABLE V.  
*Proportion of Light and Heavy Seed from Five Individual Plants.*

Number of plant	Light				Heavy			
	Weight		Volume		Weight		Volume	
	Gms.	Per cent.	Cc.	Per cent.	Gms.	Per cent.	Cc.	Per cent.
15	6.26	62.6	11.6	65.2	3.74	37.4	6.2	34.8
47	5.46	54.6	10.9	58.9	4.54	45.4	7.6	41.1
41	7.98	79.8	16.0	84.7	2.12	21.2	3.0	15.3
11W	7.90	79.0	15.4	83.7	2.10	21.0	3.0	16.3
14	5.34	53.4	10.0	56.2	4.66	46.6	7.8	43.8

There appears to be a considerable difference in the proportion of light and heavy seeds in the above individuals, while in all of them the proportion of heavy seeds is considerably greater than in the

general lot used in testing the method of separation. Table VI shows the weight of 500 of the light and the heavy seeds from the five individual plants.

TABLE VI.  
*Weight of 500 Each of Light and Heavy Seeds from Individual Plants.*

Description	Weight (Gms.)				
	No. 15	No. 47	No. 41	No. 11W	No. 14
Light.....	0.4606	0.4101	0.4757	0.5161	0.4409
Heavy.....	0.5105	0.4611	0.5288	0.5610	0.4646

To test the relative germinating power of the light and heavy seeds, fifty of each were sown in five different pots, one for each of four individual plants. Table VII shows the germination at various stages.

TABLE VII.  
*Relative Germination of Light and Heavy Seeds from Four Individual Plants. Seeds Sown April 13th.*

Number of plant	Description of seed	Germination							
		Number				Per cent.			
		May 8	May 15	May 22	May 29	May 8	May 15	May 22	May 29
47.....	Light	3	7	7	8	6	14	14	16
	Heavy	19 *	24	24	24	38	48	48	48
41.....	Light	3	5	5	5	6	10	10	10
	Heavy	3	8	12	14	6	16	24	28
11W.....	Light	4	5	5	6	8	10	10	12
	Heavy	9	21	24	26	18	42	48	52
14.....	Light	0	1	1	1	0	2	2	2
	Heavy	27	31	32	32	54	62	64	64

The results show conclusively that the light seed is mostly dead, only a small percentage of it germinating. Figure 3 shows graphically the progressive germination in each case.

#### RELATION OF COLOR OF THE SEED TO THE GERMINATION.

Belladonna seeds are either of a rich brown or silver gray color. That a relationship might exist between color and weight was con-

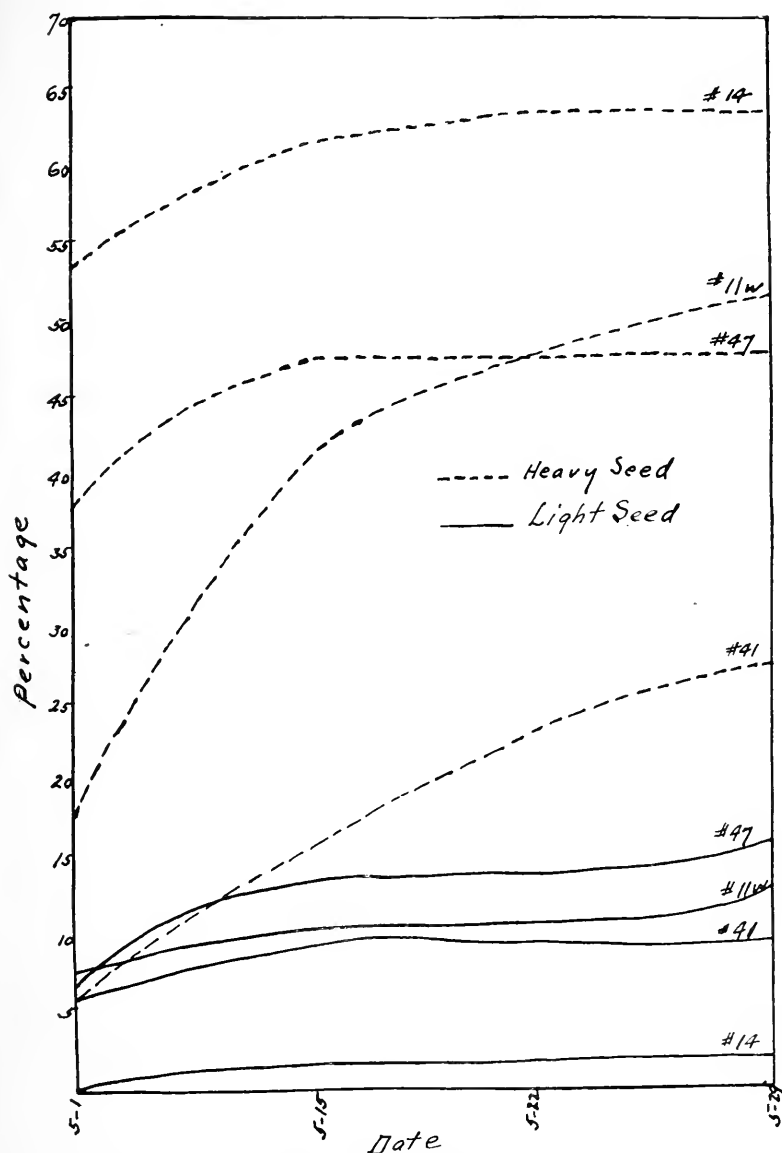


FIG. 3.—Curves showing comparative germination of light and heavy seed from four individual plants.

sidered probable, and for that reason the lots of 500 seeds each used to determine the relative weights of light and heavy seeds as given in Table VI were separated into the brown and gray, with the following result:

TABLE VIII.

*Relative Number of Brown and Gray Seed Among the Light and Heavy Seed from Five Individual Plants.*

Number of plant	Light				Heavy			
	Brown		Gray		Brown		Gray	
	Number	Per cent.	Number	Per cent.	Number	Per cent.	Number	Per cent.
15	37	7.4	463	92.6	387	77.4	113	22.6
47	397	79.4	103	20.6	471	94.2	29	5.8
41	86	17.2	414	82.8	39	7.8	461	92.2
14	460	92.0	40	8.0	500	100	0	0.0
11W	65	13.0	435	87.0	241	48.2	259	51.8
Average	209	41.8	291	58.2	328	65.6	172	34.4

Evidently there is no definite relation between color and weight, as the results show a great variation. According to the average, it appears that the heavy seeds contain a noticeably larger percentage of brown ones than the light seeds. From this one would judge that the brown seeds are of a better quality and would show a greater percentage of germination. To determinate whether such is the case, 100 seeds of the two colors were sown in pots on April 13th, with the result as indicated in Table IX following.

TABLE IX.

*Relative Germination of Brown and Gray Seeds Sown April 13th.*

Description	Germination			
	May 8 Per cent.	May 15 Per cent.	May 22 Per cent.	May 29 Per cent.
Brown.....	13	28	42	45
Gray.....	28	42	53	56

These results are quite contrary to what was expected. Table VIII shows that the heavy seed from plant No. 14 contained no grays whatever, while the light seed from the same plant was almost all gray. Reference to Figure 3 shows that the heavy seed ger-



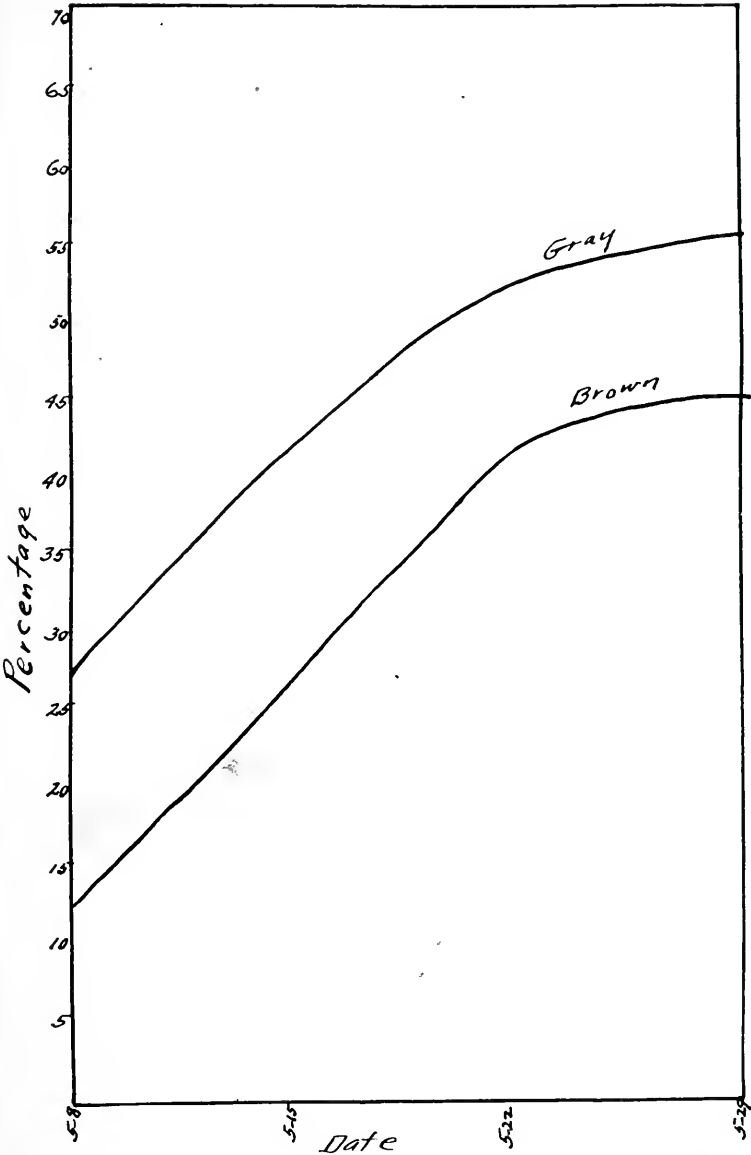


FIG. 4.—Curves showing comparative germination of gray and brown seed.

minated much better than the light. From this it would seem to follow that the brown seeds were much superior to the grays, but, in view of the results obtained from the test, it must be concluded that there is no definite relation between the color and the germinating power. Figure 4 will serve to bring out more clearly the results of the test.



FIG. 5.—Plants from 300 large belladonna seeds seven weeks after sowing.

#### TREATMENT OF THE SEEDS WITH SULPHURIC ACID.

Probably the most striking and, at the same time, most undesirable characteristic of the germination of belladonna seed is the lack of uniformity it displays. The first seeds usually begin to ger-

minate in about three weeks after sowing. The bulk of the seeds germinate between the fourth and fifth week. After that the progress is slow, a few per cent. of the total appearing every week for probably several months. Figure 5 illustrates this lack of uniformity in germination.

It has often been observed that new plants will appear after the others sown at the same time are seven to eight inches high. In some cases this might be due to lack of uniformity in sowing as regards character and condition of soil and depth of soil covering the seed. This might be especially true when sowing in the field. In greenhouse work, however, such conditions are generally avoided, and a different explanation must be found. It was thought that possibly these slowly germinating seeds might be what are generally known as "hard-heads," that is, seeds with such heavy outer walls that the necessary warmth and moisture essential to germination can penetrate but slowly. It is well known that with such seeds germination can sometimes be hastened by treating them with some substance like strong corroding acids that will partly disintegrate the outer covering of the seed. Such treatment, of course, is fatal if allowed to go too far.

Miller <sup>1</sup> found concentrated sulphuric acid beneficial when applied for a period ranging from five to fifteen minutes, the ten-minute application giving by far the best results. He does not state, however, the actual percentage of germination obtained by means of the treatment. T. B. Young found a five-minute treatment with concentrated sulphuric acid very beneficial, but concluded that a ten-minute treatment would be too long. Here again data as to the actual percentage of germination are not available.

To obtain further information on this subject, belladonna seed was subjected to sulphuric acid of various strengths and for various periods as shown in Table X.

A convenient quantity of seeds were treated for the required length of time with acid of the desired strength in a small beaker and then quickly transferred to a Gooch crucible attached to a vacuum flask and rapidly and repeatedly washed with water. They were then dried by pulling air through the crucible.

To determinate the relative germination of these treated seeds,

<sup>1</sup> Miller, Fred A., "The Propagation of Medical Plants," *Bulletin of the Torrey Botanical Club*, vol. 41, No. 2, pp. 105-136.

TABLE X.

*Showing Strength of Acid Used, Time of Treatment, and Designation of the Seed in Each Case.*

Strength of acid Per cent.*	Time treated			
	1 minute	10 minutes	30 minutes	60 minutes
92.5	A <sub>1</sub>	A <sub>2</sub>	A <sub>3</sub>	A <sub>4</sub>
75	B <sub>1</sub>	B <sub>2</sub>	B <sub>3</sub>	B <sub>4</sub>
50	C <sub>1</sub>	C <sub>2</sub>	C <sub>3</sub>	C <sub>4</sub>
25	D <sub>1</sub>	D <sub>2</sub>	D <sub>3</sub>	D <sub>4</sub>

\* By volume.

TABLE XI.

*Relative Germination of Seeds Treated with Sulphuric Acid and Sown on March 31st.*

	Germination									
	Number					Percentage				
	4-24	5-1	5-8	5-15	5-22	4-24	5-1	5-8	5-15	5-22
A <sub>1</sub> .....	1	7	26	29	32	1.66	11.6	43.3	48.3	53.3
A <sub>2</sub> .....	9	22	35	35	35	15.0	36.6	58.3	58.3	58.3
A <sub>3</sub> .....	2	3	3	3	3	3.3	5.0	5.0	5.0	5.0
A <sub>4</sub> .....	0	0	0	0	0	0	0	0	0	0
Total..	12	33	65	68	70	51.	17.8	27.1	28.3	29.2
B <sub>1</sub> .....	0	4	24	26	29	0	6.6	40.1	43.3	48.3
B <sub>2</sub> .....	1	11	34	34	34	1.66	18.3	56.6	56.9	56.6
B <sub>3</sub> .....	5	14	30	30	30	8.3	23.3	50.	50.	50.
B <sub>4</sub> .....	0	2	3	3	3	0	3.3	5.	5.	5.
Total..	6	31	91	93	96	2.5	13.	37.9	38.7	40.
C <sub>1</sub> .....	0	2	26	34	39	0	3.3	43.3	56.6	65.
C <sub>2</sub> .....	0	9	37	38	41	0	15.	61.6	63.3	68.3
C <sub>3</sub> .....	0	5	26	31	31	0	8.3	43.3	51.6	51.6
C <sub>4</sub> .....	0	2	19	23	24	0	3.3	31.6	38.3	40.
Total..	0	18	108	126	135	0	7.5	45	52.5	56.2
D <sub>1</sub> .....	0	4	26	26	26	0	6.6	43.3	48.3	48.3
D <sub>2</sub> .....	0	4	25	28	28	0	6.6	41.6	46.6	46.6
D <sub>3</sub> .....	0	6	34	36	36	0	10.	56.6	60.	60.
D <sub>4</sub> .....	0	7	25	25	26	0	11.6	41.6	41.6	48.3
Total..	0	21	110	115	116	0	8.75	45.8	47.9	48.3

sixty of each were placed in pots on March 31st. Table XI shows the result.

These results seem to demonstrate a number of facts. The

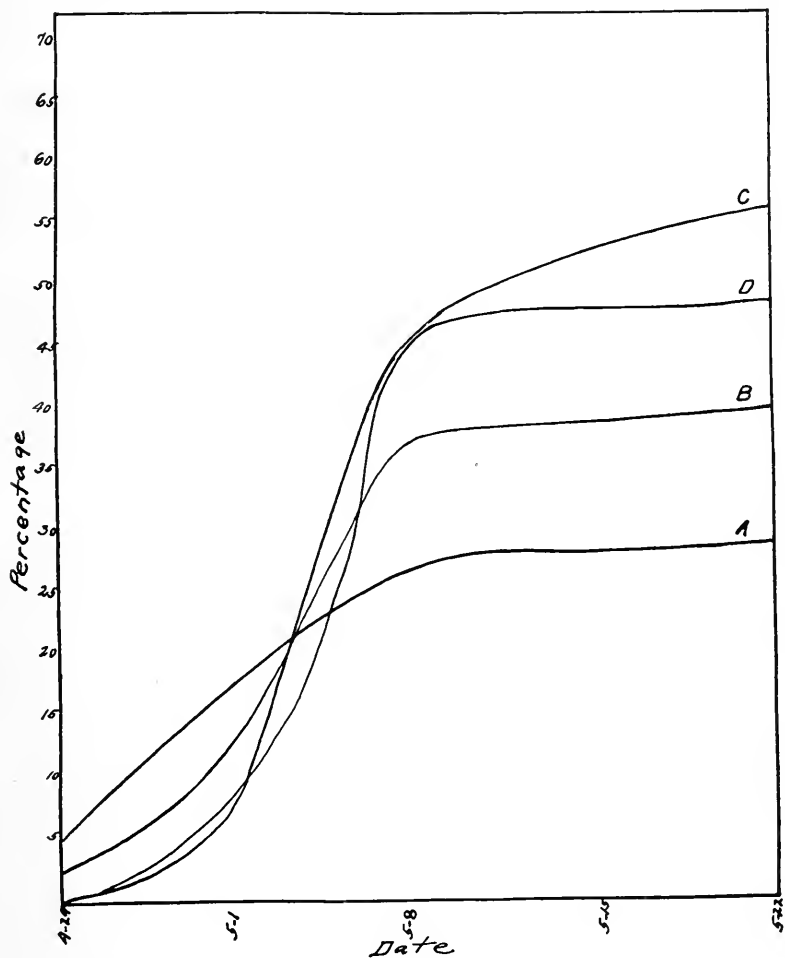


FIG. 6.—Curves showing comparative germination of all seeds treated with sulphuric acid of 92.5 per cent. (A), 75 per cent. (B), 50 per cent. (C), and 25 per cent. (D). Seeds were sown March 31st.

effect of the acid treatment as conducted in this experiment is of little practical value, the only benefit derived being that of a slight acceleration in germination. The total germination is not found to be any greater, on the whole, than in the case of seeds not subjected

to the treatment. It is evident that contact with concentrated (92.5 per cent.) sulphuric acid destroys the germinating power almost completely if continued longer than ten minutes. Treatment with 75 per cent. acid may be continued for thirty minutes without injury, which is also true of the 50 per cent. acid. When the acid is below 50 per cent. the time of contact up to one hour seems to be immaterial. It is noteworthy that only the seeds treated with concentrated and 75 per cent. acid showed any germination on April 24th, twenty-four days after sowing. In the following week, however, the seeds which received treatment with the 50 and 25 per cent. acids showed about the same germination as the others, and from then on they continued to show to better advantage.

In order to indicate more clearly what concentration of acid and what length of treatment are the most desirable, the data are arranged in the following tables.

TABLE XII.

*Total Germination of all Seeds Treated with 92.5, 75, 50, and 25 Per Cent. Sulphuric Acid for Different Lengths of Time.*

Treatment	Germination									
	Number					Per cent.				
	4-24	5-1	5-8	5-15	5-22	4-24	5-1	5-8	5-15	5-22
A <sub>1</sub> A <sub>2</sub> A <sub>3</sub> A <sub>4</sub> .	12	33	65	68	70	5	17.8	27.1	28.3	29.2
B <sub>1</sub> B <sub>2</sub> B <sub>3</sub> B <sub>4</sub> .	6	31	91	93	96	2.5	13	37.9	38.7	40.
C <sub>1</sub> C <sub>2</sub> C <sub>3</sub> C <sub>4</sub> .	0	18	108	126	135	0	7.5	45	52.5	56.2
D <sub>1</sub> D <sub>2</sub> D <sub>3</sub> D <sub>4</sub> .	0	21	110	115	116	0	8.75	45.8	47.9	48.3

TABLE XIII.

*Total Germination of all Seeds Treated for 1, 10, 30, and 60 Minutes with Sulphuric Acid of Various Strengths.*

Treatment	Germination									
	Number					Per cent.				
	4-24	5-1	5-8	5-15	5-22	4-24	5-1	5-8	5-15	5-22
A <sub>1</sub> B <sub>1</sub> C <sub>1</sub> D <sub>1</sub>	1	17	102	115	126	0.4	7.	42.5	47.9	52.5
A <sub>2</sub> B <sub>2</sub> C <sub>2</sub> D <sub>2</sub>	10	46	131	135	138	4.2	19.2	54.6	56.2	57.5
A <sub>3</sub> B <sub>3</sub> C <sub>3</sub> D <sub>3</sub>	7	28	93	100	100	2.9	11.7	38.7	41.7	41.7
A <sub>4</sub> B <sub>4</sub> C <sub>4</sub> D <sub>4</sub>	0	11	47	51	53	0.0	4.5	19.5	21.2	22.1

# TREATMENT OF SEEDS WITH HYDROGEN PEROXIDE.

It has been found that hydrogen peroxide has an accelerating influence on the germination of a large number of seeds, and for that reason the following experiment was undertaken to determine

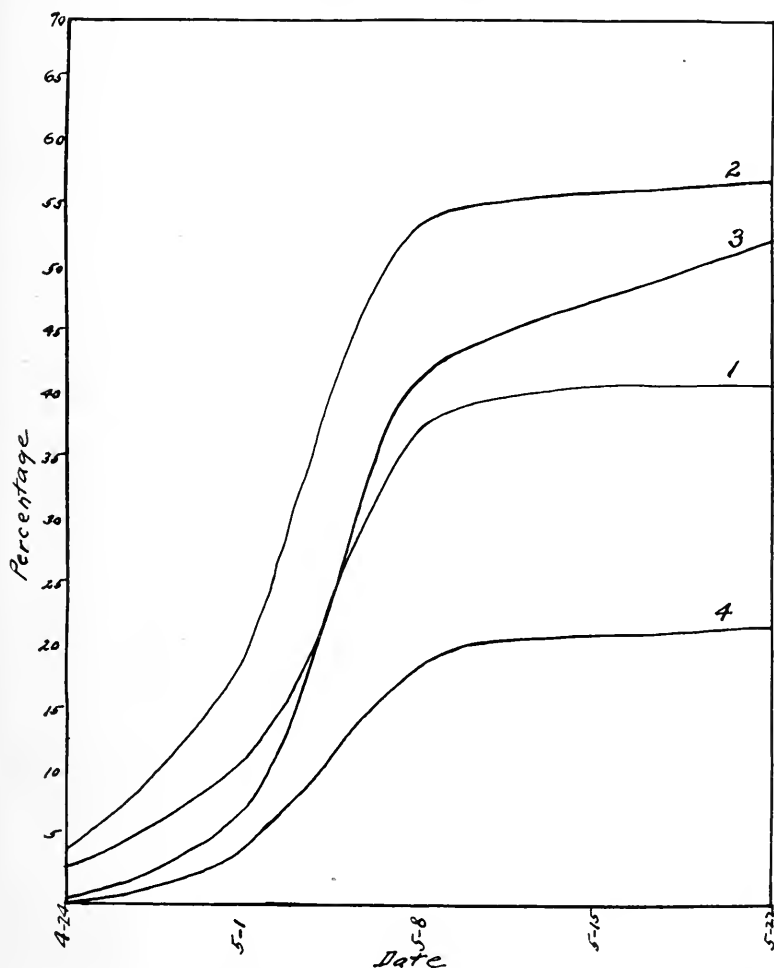


FIG. 7.—Curves showing comparative germination of all seeds treated with sulphuric acid for 1 minute (1), 10 minutes (2), 30 minutes (3), and 60 minutes (4). Seeds were sown March 31st.

whether belladonna seed yielded to such treatment. The hydrogen peroxide used was the commercial kind containing 40 per cent. of absolute peroxide. This strength is designated in the tabulations

as 100 per cent. The weaker solutions designated as 80, 60, 40, and 20 per cent. in the tabulations were made by diluting the commercial material on the basis of 100 per cent. A small lot of the seeds was treated with the various solutions of peroxide for 18 hours. The treatment was duplicated with another lot of seeds for 24 hours and with still another lot for 48 hours. All seeds were immediately dried after the removal of the peroxide in a Gooch crucible. One hundred seeds of each lot were planted on February 16th and the germination noted from time to time. Table XIV shows the percentage of germination in each case up to April 9th, when the germination appeared to be completed.

TABLE XIV.

*Comparative Germination of Seeds Treated with Hydrogen Peroxide and Sown February 16th.*

Time of treatment	Strength of hydrogen peroxide used per cent.	Percentage of germination				
		March 13	March 19	March 25	April 2	April 9
18 hours.....	20	11	31	32	34	35
	40	18	56	60	64	64
	60	19	63	66	69	69
	80	13	61	62	65	67
	100	14	29	35	40	41
24 hours.....	20	32	52	58	59	59
	40	22	60	68	70	70
	60	18	39	48	52	52
	80	28	36	40	44	44
	100	27	39	40	44	45
48 hours.....	20	17	41	49	50	55
	40	12	24	29	34	39
	60	34	54	55	60	60
	80	23	49	53	55	56
	100	16	37	39	43	44

TABLE XV.

*Total Number Germinated of all Seeds Treated for 18, 24, and 48 Hours, Respectively.*

Time of treatment	Number of seeds germinated out of 500				
	March 13	March 19	March 25	April 2	April 9
18 hours.....	75	240	255	272	276
24 hours.....	127	226	254	269	270
48 hours.....	102	205	225	242	254



Figures 8 and 9 show graphically the effect of the treatment with peroxide, both as to the strength of the solution used and the time of treatment.

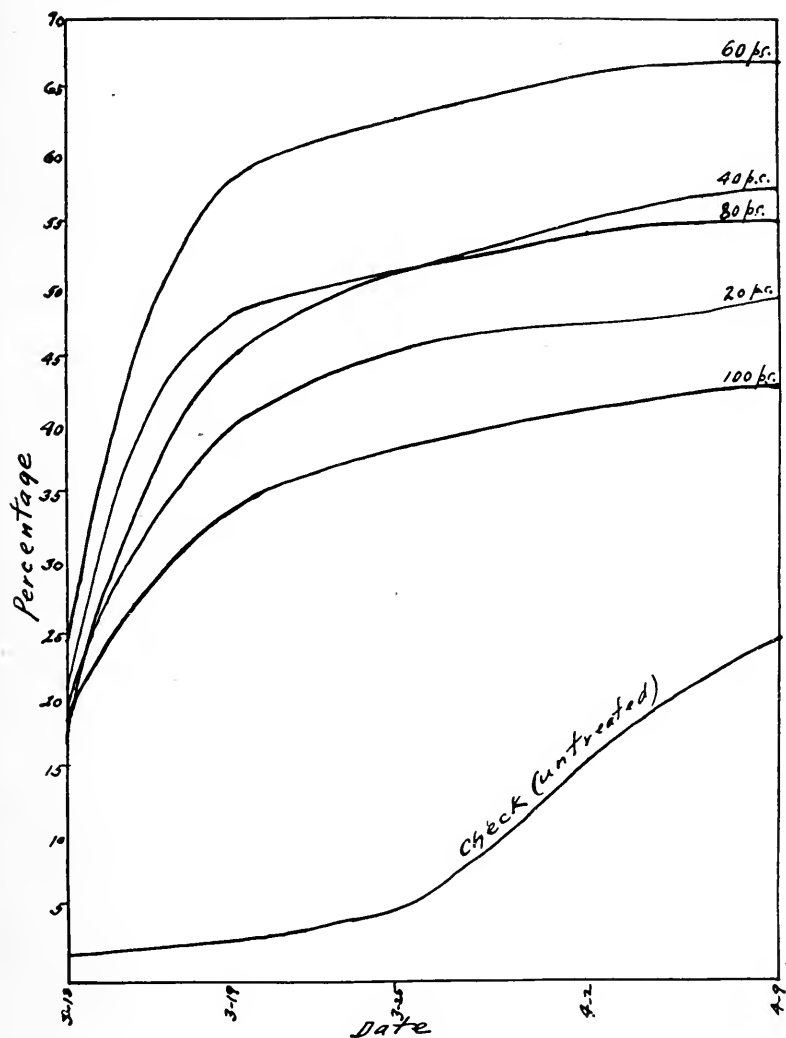


FIG. 8.—Curves showing the comparative germination of all seeds treated with hydrogen peroxide of 20, 40, 60, 80, and 100 per cent. strength. Seeds sown on February 16th.

It is evident that the treatment with hydrogen peroxide is of very appreciable benefit. The percentage of germination during the first four or five weeks, when compared with that of the untreated seeds

used as a check, is much greater than was expected. It appears, from the check, that this lot of seeds would be especially slow in germinating under ordinary conditions, though the total germination would

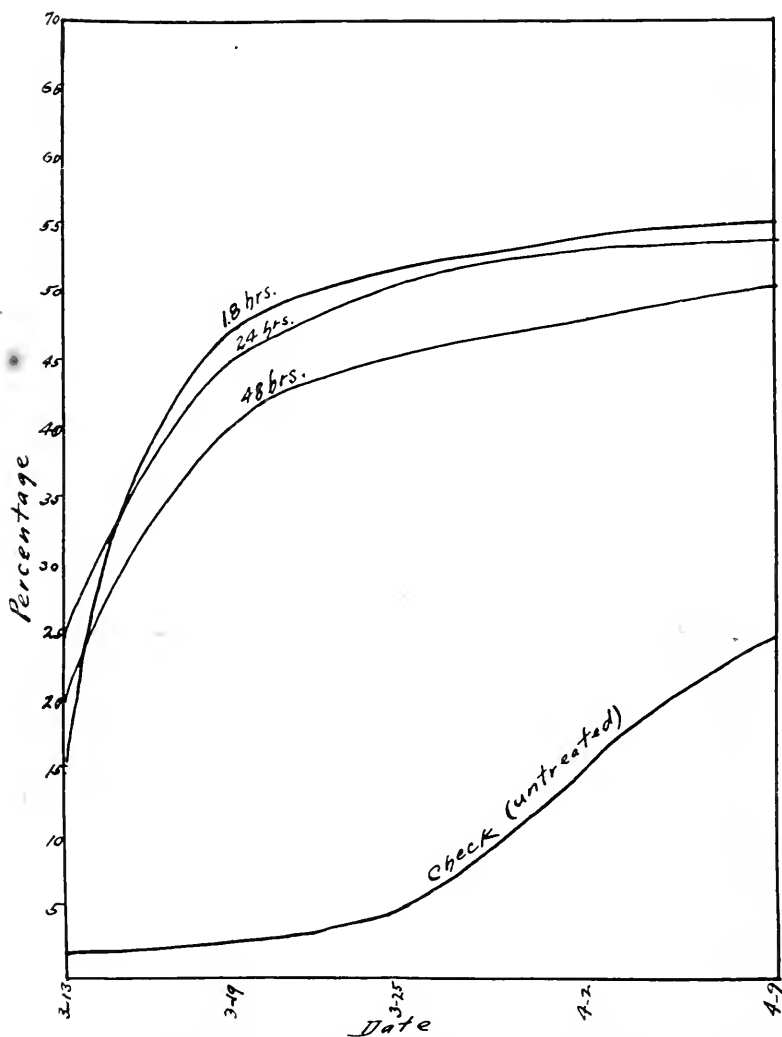


FIG. 9.—Curves showing the comparative germination of all seeds treated with hydrogen peroxide for 18, 24, and 48 hours. Seeds sown February 16th.

probably compare favorably with the usual average. The maximum germination secured by the peroxide treatment was 70 per cent., while the minimum was 35 per cent. Taken as a whole, the effect

of the peroxide seems to have been to induce a uniformity in the germination rather than an acceleration or an actual increase in percentage. From these experiments and from those with sulphuric acid it seems that when working under conditions such as those described the effect of treating the seeds with chemicals is to induce a uniformity or spontaneity in the germination. The seeds, however, seem to require as much time to begin germination as the untreated seeds.

As regards the concentration of the peroxide used, it is evident that neither the concentrated nor the greatly diluted material is of as much benefit as the medium strengths. It will be seen from Figure 8 that the 60 per cent. solution gave the best results. The 80 and 40 per cent. solutions gave results very much alike, while the 20 and 100 per cent. solutions had the least effect.

The time of treatment does not seem to make any great difference. The 18- and 24-hour treatment gave very similar results, while the 48-hour treatment was not quite so effective. It is evident that there is no benefit in treating the seeds longer than 18 hours, and it is possible that a shorter period would be just as effective.

#### THE EFFECT OF SCRATCHING THE SEED COATS.

Many seeds germinate very slowly, owing to their hard and thick coats, which do not admit of a rapid permeation of moisture and air into the seed. Such seeds have often been benefited by scratching the surface by some mechanical means, so as to hasten the absorption of moisture, with a consequent acceleration of the germination.

To determine the effect of such methods on belladonna seeds, a quantity of the seed was shaken in a bottle with powdered glass for one and a half hours. Another quantity was rubbed gently between two sheets of fine emery paper. One hundred seeds from each lot were planted as a test. The following table shows the result:

TABLE XVI.

*Comparative Germination of Belladonna Seed Scratched with Powdered Glass and Emery Paper. Seeds Sown February 16th.*

Treatment of seed	Percentage of germination					
	March 13	March 19	March 25	April 2	April 9	April 16
Check (untreated).....	2	3	5	16	25	33
Shaken with powdered glass.	3	18	21	34	45	47
Rubbed with emery paper...	0	11	17	22	26	28

The effect of scratching does not appear to be as great as was expected. The shaking with sand gave better results than the emery treatment. Figure 10 shows the results graphically.

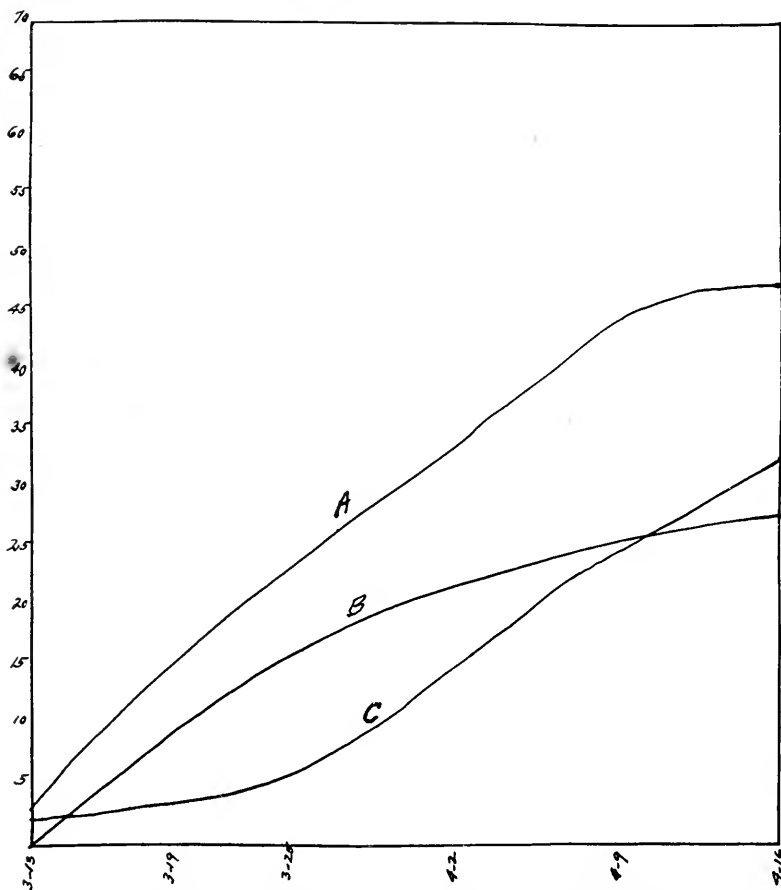


FIG. 10.—Curves showing effect of scratching seed coats. (A) Seeds shaken with powdered glass; (B) seeds rubbed between emery paper; (C) check. Seeds sown February 16th.

#### SUMMARY.

The subjection of belladonna seed to freezing temperatures accelerates their germination. Hence it is of benefit to sow the seed in the fall in order to insure a rapid and early germination in spring.

There appears to be no relationship between the size of the seed and its germinating power. This must not be taken to indicate that a relationship does not exist between the size of the seed and the vigor and strength of the plant.

The heavy seeds are by far the best. The percentage of germination of the light seeds is very small. Separation of these inert seeds can be readily effected by immersing the seed in water and discarding those which do not sink. The proportion of light and heavy seed from each individual plant varies greatly. This may be due partly to carelessness in picking the berries, as unripe berries contain light and worthless seeds. The question of drying is also of importance. The berries must be thinly scattered and dried in a well-ventilated room, in order to reduce molding to a minimum. It is probable that a certain percentage of the seed in a fully developed berry is inert, which would account to some extent for the relatively low percentage of germination of the average belladonna seed.

Color appears to be no criterion of the value of the seed as regards germinative power. The brown seeds have a better appearance, but apparently the gray ones have equal vitality.

While other investigators have found that treatment with concentrated sulphuric acid from one to ten minutes is of benefit, experiments with various strengths of acid for periods ranging from one to sixty minutes showed that, as a whole, the treatment is not of any great value. The germination was accelerated in some instances, but no material increase in actual germination was noted.

Treating seeds with hydrogen peroxide was found to be of very material benefit. Eighteen and twenty-four hours gave better results than longer treatment. A 60 per cent. solution of the commercial hydrogen peroxide gave the best results. The concentrated solution was the least beneficial.

Scratching the seed coats by shaking in a bottle with powdered glass and by rubbing between sheets of emery paper, while of some benefit, was not nearly as beneficial as the peroxide treatment.

## MEDICINAL PLANT GARDENS.\*

By DR. W. W. STOCKBERGER, Physiologist in Charge of Drug-Plant and  
Poisonous-Plant Investigations, Bureau of Plant Industry, United  
States Department of Agriculture.

It is not my intention in this paper to present a descriptive account of medicinal plant gardens in general, or even to discuss the more important ones of this country, except in so far as reference to them may be necessary by way of illustration. I shall endeavor, however, to point out what to me appear to be some popular misconceptions concerning the scope and function of such gardens, and to suggest how they may be made to increase their usefulness to *Materia Medica* and *Pharmacognosy*.

For the purpose of this discussion, medicinal plant gardens may be regarded as falling under one of two general classes, the first being pedagogic, the second industrial. The pedagogic garden is, naturally, an adjunct of a school of pharmacy or of a botanic garden. Its scope includes all medicinal plants that are adapted to existing soil and climatic conditions, supplemented by greenhouse facilities. Its function is to familiarize students with the habit and appearance of the entire living plant, some part of which is used as a plant drug, to supply the need for authentic specimens for observation and demonstration in the classroom, and to furnish materials for research work on the morphology and chemical constituents of drug plants. Necessarily it will be found desirable to grow a large number of species in this type of garden, but, owing to the cost of maintenance, the space which can be devoted to any one species will be very small.

The industrial garden, on the other hand, is an adjunct of public or private enterprise, the object of which is to give additional information concerning our agricultural resources. Its scope is the same as that of the pedagogic garden, but it differs very materially in function, which is to serve for the determination of the adaptability of medicinal plants, not only to soil and climatic conditions, but to economic conditions as well. In the industrial garden a large number of species will be tested on a small scale to determine whether the soil and climate are suitable for their growth; then the

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\* A paper read before the Scientific Section of the A. Ph. A. at the Detroit meeting, 1914.

few promising ones must be tried out on an area large enough to yield reliable data on the actual conditions of commercial production. A considerable acreage of land is indispensable for this type of garden if the results secured therein are expected to have much economic significance.

There is no lack of evidence that the general public often, if not as a rule, fails to differentiate the functions of the pedagogic and industrial gardens, since advice is freely sought from both regarding the production of medicinal plants for the sole purpose of deriving profit therefrom. It is also an open question whether this distinction in function is in every case clearly understood by those responsible for the management of medicinal plant gardens. Statements sometimes unguarded, or not properly qualified, and sometimes based upon inconclusive and insufficient data, have on several occasions inspired the imagination of writers for the popular magazines or daily press, and, as a result, visions of large and easy profits have been portrayed under various alluring titles, as, for example, "Big Profit from Drug Weeds," "The Herb Grower Has a Chance at an \$18,000,000 Business," "A Profit of One Hundred Dollars per Acre from Growing Medicinal Weeds." Moreover, the widespread interest in the possibility of growing medicinal plants for profit which has been developed in this country during the past decade has been capitalized by a number of crafty promoters, who use the mails and the columns of journals and magazines to disseminate flamboyant advertisements of the enormous profits which may be made by growing certain medicinal plants. Frequently the name of the plant is withheld until the victim has remitted from one to five dollars, for which he receives practically valueless instructions for the cultivation of some plant poorly adapted to our economic conditions. A typical get-rich-quick scheme of this class is explained thus: "It has to do with a certain plant which grows like a weed; it is cut and cured like hay and sells for 45 cents per pound, which is at the rate of \$900 per ton." The investment of one dollar brings the name of the herb, with the further information that the product of one acre will sell for \$1800! As a matter of fact, the commercial cultivation of this plant is almost unknown in the United States, and there is yet no established market for the American product.

These illustrations will account for the doubt which has arisen

in my mind as to the propriety of purely pedagogic gardens being used as a basis for generalizing on the question of drug growing for profit. In agricultural experimentation it is well recognized that the results from small trial plots must be interpreted with due regard for the large factor of error, which is always present. With proper care and attention it is relatively easy to grow a luxuriant crop of any one of a number of drug plants on a square rod of good garden soil, but what can be done under ordinary agricultural conditions on one or more acres can not be calculated therefrom by "a simple sum in arithmetic," as one writer has naïvely said.

There are numerous well-authenticated instances in which the production of some medicinal plant has resulted in a fair profit, but there is yet no evidence at hand to justify the belief that satisfactory results can be secured without some practical experience in gardening, some knowledge of the requirements of crude drugs, and due regard for economic conditions.

Every pharmacist and physician is, or should be, interested in obtaining crude drugs of highest quality and standard efficiency, but material progress toward the attainment of this end will not be favored by encouraging a large number of persons to become small producers. The result of small individual collections, varying widely as to time, place, and method of gathering, is seen in the miscellaneous aggregates all too frequently found in our crude drug markets, and unless a perpetuation of this condition is desirable, little encouragement should be given to the suggestion that whoever has a small back yard available may become a producer of plant drugs.

The educational opportunity open to the pedagogic gardens is almost limitless. The dissemination of knowledge to countless individuals not having access to the garden itself regarding the history, geographic distribution, methods of preparation, and uses of crude drugs may be accomplished through illustrated lectures and carefully prepared articles written for the less technical periodicals. Such misconceptions as, for example, that the production of ipecac in New England and vanilla beans in Iowa is a commercial possibility, or that stramonium is produced by a "melon weed," are all too prevalent and should be corrected. But educational work along this line deserves little tolerance unless inspired by some motive more commendable than that of merely arousing interest in growing



drug plants, otherwise the whole movement will sooner or later be discredited. Recently a reputable pharmaceutical journal published an article in which the writer set forth at some length the possibilities for the commercial production of a certain drug plant in the Southwest. A request for further information brought forth from this writer the astounding statement that he had no personal knowledge of conditions in the Southwest, but, *having grown this plant in one of the northern States*, he saw no reason why it should not be profitably grown in the Southwest, "on rocky and otherwise unprofitable land, on hillsides or arid desert soil." In this case the motive was evidently merely the arousing of interest, and the writer mentioned displayed a fine disregard for the practical difficulties attending the growing of the plant in question, which sharply localize the areas on which it may be economically produced.

The time is certainly ripe for injecting into discussions and recommendations regarding the cultivation of medicinal plants some of the sanity and discrimination which characterizes conservative business operations. Such a course is necessary if the interest already aroused is to be retained and directed along lines productive of beneficial results. It should be remembered that the expense of agricultural operation varies widely according to location. In some localities the outlay for farm labor will be three and one-half times as much as in others. Sometimes we find a low expense for labor associated with a heavy outlay for fertilizers, sometimes heavy expense for both labor and fertilizers, and, again, low expense for both. The complications introduced by these factors alone render it practically impossible to make any safe general statement as to the profitableness of drug growing. Furthermore, two localities separated by a distance of less than fifty miles may present a totality of conditions so different that a drug-growing enterprise which could probably be conducted at a profit in the one would with equal probability fail absolutely in the other.

I do not wish to be understood as taking the position that there is no opportunity in the cultivation of medicinal plants, for I have abundant evidence that, given the *necessary favorable conditions*, a fair return may be expected from several drug crops. On the other hand, I also have abundant evidence that hundreds of persons have received the impression that drug crops can be grown by anybody anywhere at a profit far in excess of that to be obtained from ordi-

nary cultivated crops. I am convinced that in some cases optimism and enthusiasm have been allowed to outrun common sense, but if, in the future, due consideration is given to the fundamental principles of agricultural economics, I believe that a rational attitude toward commercial drug-plant cultivation may be developed.

The founders of the several excellent pedagogic gardens which are now maintained in connection with certain schools of pharmacy have inaugurated a movement which promises much for the future of *Materia Medica* and *Pharmacognosy*. It is sincerely to be hoped that their example will lead to the establishment of such gardens in connection with each of the 75 or more schools of pharmacy in the United States, and to an extension of the scientific study of medicinal plants. The problems demanding attention are very numerous, but some of the lines of study and investigation which need to be emphasized are those concerning the adaptation and acclimatization of medicinal plants, the conditions under which the active principles of plants are formed, and the behavior of the plants themselves under varying conditions of climate and culture. Moreover, the selection and breeding of medicinal plants not only promises to yield results of great practical importance, but also affords a field for the widest scientific activity.

It is to be regretted that at present there is no satisfactory way in which the investigations being made upon medicinal plants in different sections of this country can be properly correlated and reduced to form for definite comparison. Especially desirable is a practical basis of correlation for studies of the variation in plant constituents, due in part, at least, to differences in geographical location. When two more or less widely separated workers attempt to compare the results of their studies, it frequently happens that they experience the greatest difficulty in harmonizing their results. This is due in part to differences in the response which plants make when under different environmental conditions, in part, probably, to variations in the method of procedure followed in the cultivation, curing, and analysis of the plant, and in part, no doubt, to differences in the genetic relationship of the plants studied by the respective investigators.

There seems to be an opportunity for some arrangement or mutual agreement between the representatives of our various medicinal plant gardens under the terms of which multiply samples of seeds

or plants of common parentage could be distributed for the production of plants to be used experimentally. If under such an agreement uniformity of treatment throughout the processes of culture, curing, and analysis could be secured, comparison of results would be much more profitable than at present, and the tabulation and summarizing of the results of experimental work conducted along the lines indicated in a number of localities would permit the drawing of conclusions having a significance far greater than those that can be reached by a single isolated worker. The suggestions here offered contemplate nothing like a general coöperative investigation, but rather the adoption of what might be regarded as a standard method of procedure analogous to official methods of analysis, etc. The tabulation and summarizing of results might well follow individual publication, as no other course is likely to give satisfaction.

In conclusion, I wish to say that the resources of the experimental drug gardens of the Office of Drug-Plant Investigations, Bureau of Plant Industry, are open to any school of pharmacy desirous of starting a medicinal plant garden, as are also the facilities of that office for effecting the distribution of material for experimental purposes, and for furthering the collection and compilation of data on the cultivation of medicinal plants under great diversity in conditions of growth.

BUREAU OF PLANT INDUSTRY,  
United States Department of Agriculture,  
August 18, 1914.

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## A STUDY OF SOME OF THE METHODS FOR THE DETERMINATION OF CALOMEL IN CALOMEL TABLETS.

By J. W. MARDEN and O. E. CUSHMAN.

In the determination of calomel in calomel tablets there is a choice of several methods of procedure. Since the composition of calomel tablets varies considerably, different methods apply better to some samples than to others, and care must be exercised in selecting a method which will give correct results: many fillers, such as talc, sodium bicarbonate, gum acacia, confection of rose, etc., are often found.

Possibly the most widely used method for the analysis of mercurous mercury is the gravimetric estimation as the sulphide.<sup>1</sup> In this

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<sup>1</sup> Treadwell-Hall, *Anal. Chem.*, vol. ii, p. 168; Olsen, *Quant. Chem. Anal.*, p. 79.

method it is necessary to oxidize the mercury in order to get it into solution, and for this oxidation strong acids, aqua regia, free chlorine, or some other suitable reagents are commonly used. When the mercury is completely oxidized the strong acids are nearly neutralized and the clear solution treated with hydrogen sulphide. The mercuric sulphide thus precipitated always contains free sulphur, and this must be removed before the sulphide can be dried and weighed. The precipitate is therefore washed thoroughly with dilute hydrogen sulphide water and finally washed repeatedly with carbon disulphide to remove the free sulphur.

There are at least three objectionable points in this method. First, the length of time required for a determination (which depends, of course, upon the modification used) is much too long for the average analyst. Second, the difficulty of obtaining complete oxidation is very great. Certain fillers seem to add to this difficulty, and talc, if it is present, remains suspended in the solution. In such a case there is no way of determining when the reaction is complete. The use of strong acids for the oxidation is inadvisable because of the difficulty in removing the excess of acids before the precipitation of the sulphide, and, according to Treadwell, the nitric acids in the aqua regia, if this is used, can not be removed by evaporation because of the volatility of the mercuric chloride. It was found that oxidation with free chlorine in alkaline solution is the most successful, as the proper degree of acidity for complete precipitation with hydrogen sulphide is more easily attainable here than in the methods employing concentrated acids. Third, although a number of modifications of this method have been suggested for the extraction of the free sulphur with carbon disulphide, none of these have been found to give very satisfactory results. It is apparent that it is very difficult to wash out occluded sulphur from precipitates unless they are finely divided. Mercuric sulphide precipitates, under ordinary circumstances, in clots which can not be easily disintegrated, and considerable experience has shown that extraction with the Soxhlet apparatus for many hours does not remove the sulphur so that the results obtained could be looked upon with confidence.

According to Merrill,<sup>2</sup> mercury can be determined by the volatilization of the mercurous chloride. In this method the procedure is, roughly, to triturate the tablets in warm water and transfer the

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<sup>2</sup> E. C. Merrill, Bureau of Chemistry, Washington, D. C. /

solid mercurous chloride to a Gooch crucible which has been previously ignited. The crucible and its contents are washed thoroughly, dried at 110° C., weighed, ignited in a Bunsen burner to drive off the mercurous chloride, cooled, and weighed again. The loss in weight is assumed to be mercurous chloride. This method is shorter and simpler than the sulphide method, but it can not be used for the analysis of certain calomel tablets. It was found in several cases that fillers consisted of some ingredients that were insoluble in water and various organic solvents, but were at the same time volatile or combustible, like cellulose, thus giving a result too high.

A method was also tried for the volatilization of the free mercury after the calomel had been reduced with formaldehyde. Here there is no means of telling when the reduction is complete, and even after considerable effort consistent results were not obtained.

Merrill also suggested a method for the reduction of mercury to the metallic state with formaldehyde, filtering off the free mercury, and determining the chlorine gravimetrically as silver chloride. This is open to the same objections as the preceding method, for complete reduction with formaldehyde is somewhat slow and difficult.

An iodine titration method<sup>3</sup> is suggested by various text-books on quantitative analysis which is rapid and gives good results with most samples of calomel, but very poor results with a few others, success seeming to depend on the character of the filler used. The method consists in treating the tablets, which have been disintegrated with water, with potassium iodide and standard iodine solution in excess, and titrating this excess with sodium thiosulphate solution. A control is run under similar conditions, and the difference between the amount of thiosulphate solution used in the control and the sample represents the iodine consumed by the calomel. The end point in this titration is not decisive and changes on standing. It was found in other cases that the iodine did not react as rapidly as the method indicated, but that after the iodine had been added it was better to allow the solution to stand before titration.

Other methods might be cited, but the above-mentioned are sufficient to indicate the difficulty of devising a method that is at once rapid, accurate, and applicable to all cases. The need for such a method arose in this laboratory by reason of the number of samples

<sup>3</sup> Schimpf, "Manual of Volumetric Analysis," p. 408; Sutton, "Methods of Volumetric Analysis," p. 248.

of calomel received for analysis and the limited amount of time available. A method was devised, which was afterward found to be identical with the method recently suggested by Kohn and Oster-setzer,<sup>4</sup> which seems to very nearly satisfy the conditions. Kohn found that the halogen compounds of mercury could be easily oxidized and made soluble by means of sodium peroxide, and the halogen titrated by Volhard's method with silver nitrate. This method, as it has been used for the results below, is as follows: The tablets, in amount corresponding to 0.2 to 1.0 gm. of Calomel, are first disintegrated in about 30 C.c. of water, made acid with nitric acid to drive off the carbon dioxide from the sodium bicarbonate, which is often used as a filler, and sodium peroxide added, a little at a time, with stirring, until the gray metallic mercury separates out. About one gramme of sodium peroxide is added in excess. After heating for a very few minutes, the precipitated mercury is filtered onto a Gooch crucible and washed with water. The filtrate is strongly acidified with nitric acid, tenth-normal silver nitrate added in excess, and the solution then cooled and agitated, causing the precipitate to coagulate.<sup>5</sup> The excess of silver nitrate is then titrated with potassium sulphocyanate, using ferric alum as an indicator. This method is rapid, requiring only a few minutes for a determination; it is simple, and it was found to give accurate results with all of the samples of calomel tablets tried.

The first table below gives a series of results of the analyses of known amounts of pure, carefully dried mercurous chloride by Kohn's method, using certified burettes for the titrations.

The second table gives the results with mixtures of calomel and sodium carbonate. This will give an idea of about how close tablets consisting of these constituents could be determined by this method.

TABLE I.

No.	Gms. HgCl	Cc. N/10 AgNO <sub>3</sub>	Cc. N/10 KCNS	Gms. HgCl found	Per cent.
1	0.5000	25.00	3.83	0.4986	99.72
2	0.5000	25.00	3.78	0.4998	99.98
3	0.5000	25.00	3.83	0.4986	99.72
4	0.5000	25.00	3.80	0.4993	99.86
5	0.5000	25.00	3.83	0.4986	99.72
Average per cent. ....					99.80

<sup>4</sup> *Zeits. anorg. Chem.*, 80, 218.<sup>5</sup> Rathmund and Burgstaller, *Zeits. anorg. Chem.*, 63, 330 (1909).

TABLE II.

No.	Gms. HgCl	Gms. Na <sub>2</sub> CO <sub>3</sub>	Cc. N <sup>10</sup> AgNO <sub>3</sub>	Cc. N <sup>10</sup> KCNS	Gms. HgCl found	Per cent found in mixtures
1	0.8000	0.2000	40.00	6.13	0.7960	79.64
2	0.8000	0.2000	40.00	6.12	0.7968	
3	0.6000	0.4000	30.00	4.61	0.5981	59.85
4	0.6000	0.4000	30.00	4.56	0.5993	
5	0.6000	0.4000	30.00	4.61	0.5981	
6	0.4000	0.6000	25.00	8.04	0.3996	39.94
7	0.4000	0.6000	25.00	8.06	0.3991	
8	0.2000	0.8000	15.00	8.48	0.1999	19.92
9	0.2000	0.8000	15.00	8.43	0.1985	

It must be admitted that the results obtained for this table are a little low, due either to a passing of the end point in the titration, or to the reverse reaction <sup>6</sup> which occurs when the silver chloride is not removed before the excess of silver nitrate is titrated.

The third table shows some of the results of the analyses of several samples of calomel tablets by the sodium peroxide method and the checks made by some of the other methods of analysis. The table is condensed, showing only the average of duplicate determinations in each case. This table is intended to give an idea of how the amount of calomel found by different methods varies with the conditions imposed by each method.

TABLE III.

No.	Grains per tablet claimed	Grains by sulphide method	Grains by volume of Hg	Grains by volume of HgCl	Grains by iodide method	Grains by Na <sub>2</sub> O <sub>2</sub> method	Per cent. of labelled value found by Na <sub>2</sub> O <sub>2</sub> method
1	1.000	0.992	....	....	....	1.030	103.0
2	1.000	0.775	....	....	....	0.870	87.0
3	0.250	0.212	0.190	....	....	0.252	100.8
4	1.000	....	1.010	....	....	0.982	98.2
5	1.000	....	1.070	....	....	1.030	103.0
6	0.250	....	0.300	....	....	0.252	100.8
7	0.500	....	....	0.529	....	0.525	105.0
8	0.250	....	....	0.333	....	0.147	98.8
9	0.250	....	....	0.208	0.260	0.204	81.6
10	0.250	....	....	0.230	0.239	0.258	103.2
11	0.500	....	....	....	0.459	0.494	98.8
12	1.000	....	....	....	1.095	0.946	94.6
Average.....							97.9

<sup>6</sup> Rosanoff and Hill, *J. Am. Chem. Soc.*, 29, 269 (1907).

It will be noted that the results by the sulphide method are somewhat low, due probably to incomplete oxidation of the calomel. The results by the reduction to metallic mercury and subsequent volatilization are variable, and by volatilization without reduction they are high, as might be expected. The last column of Table III may also be used to show how close the calomel tablets put out by good firms check their labelled values. No. 9 illustrates a case where oil is used in compounding the tablets, and the high result by the iodide method indicates a possible absorption of iodine by the oil present.

In conclusion it is important to note that no case has as yet been encountered where the sodium peroxide titration method did not give consistent results, and no trouble was found due to imperfect oxidation. Undoubtedly much of the discrepancy in results is due to the chipped condition in which the tablets were found, in some cases it being difficult to obtain the proper number of unbroken tablets. In several cases the tablets were weighed and the calomel then figured on a percentage basis, thus checking the consistency of the work of the operator. In unbroken tablets a variation of several per cent. in their weights was found, which would explain much of the variation in the last column of Table III. Briggs<sup>7</sup> considers that 15 per cent. variation in weight would not be excessive, which seems, however, to be larger than is necessary.

THE SOUTH DAKOTA FOOD AND DRUG DEPARTMENT, Vermilion.

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## IS THE PRESENT AN OPPORTUNE TIME FOR THE REVISION OF OUR PATENT LAWS IN SO FAR AS THEY AFFECT MEDICINAL AND CHEMICAL PRODUCTS?

By JOHN K. THUM, Pharmacist at the German Hospital, Philadelphia.

At the October meeting of the Philadelphia Branch of the American Pharmaceutical Association there was more or less discussion as to the advisability of urging upon Congress at this time the need of an equitable revision of our Patent Laws in so far as they relate to medicines and chemicals for the use of the sick.

There is no need at this time to enter into details as to the necessity for such revision. All well-informed pharmacists are aware of

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<sup>7</sup> Briggs, *J. Am. Phar. Assoc.*, vol. iii, 33 (1914).



the fact that foreign manufacturers have enjoyed a rich harvest for years, and waxed rich at our expense by taking advantage of these laws which give a patent on a medicinal or chemical product.

Dr. F. E. Stewart, who is chairman of the Committee on Patents and Trade Marks of the American Pharmaceutical Association, and who is recognized as an authority on such matters, was present at this meeting and in the course of the discussion mentioned that the last time he was at Washington advocating legislation along these lines a United States Senator said "that so long as the different organizations and branches of the drug trade came before Congress, each with different ideas and plans, it would be impossible for Congress to do anything. You must get together and agree as to what you want and then we can help you."

If all the different interests of the drug trade in this country were able to get together on the "Harrison Anti-Narcotic Bill," why should they not be able to get together on a matter which has for its object a just and equitable revision of our Patent Law as it affects our calling? Why not put this matter up to the National Drug Trade Conference, and have this body debate the matter thoroughly and formulate some definite plan that will be fair and just to the consumers of medicinal products in this country, to those who are responsible for them and to those various interests of our calling who must handle and distribute them?

Now is the time to push forward this great work. For years and years this question has been under more or less discussion. One could hardly attend a meeting of either a State or National Association without hearing something said about it. Its importance and necessity is conceded by everyone, so why not have the various interests act in concert? Never has American pharmacy had a more favorable and opportune time for the furthering and carrying out of a truly great piece of constructive legislation.

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## DIGITALIS AND ITS PREPARATIONS.

It is particularly encouraging to those who advocate a more rational study and intelligent administration of drugs, especially in these days when the medical profession is being bombarded on all sides with so-called newer preparations of digitalis, to know that the result of practical research work done by men who have no axes to grind is available to help along such a propaganda.

In a paper entitled "Digitalis and Its Preparations," and which might well be called "The Truth About Digitalis," Dr. Robert A. Hatcher, professor of pharmacology at Cornell University, explodes some conceptions of this drug.

Digitalis, Dr. Hatcher states, acquired a reputation as a household remedy in dropsy some time before it was introduced into medical literature. One of the earliest of writers about this drug was Dr. Withering, an English physician. This physician stated that the wild-grown drug was more active than the cultivated. This belief, Dr. Hatcher says, continues to be still accepted. It is also believed that only the leaves of the second year's growth collected at the time of flowering should be used. This claim is supported by most of the pharmacopœias of the world. How this belief originated no one knows, but it surely was the result of superficial observations, as Worth Hale and other pharmacologists have found, through experiments on animals, that leaves of the first year are more active than the average leaf of the second year. And it is very interesting to know that the leaves used in this work were from cultivated plants.

"Another curious misconception regarding digitalis which is hard to explain is that the leaf grown in certain regions is more active than that grown in other localities. It has often been stated that the Bohemian leaf is too toxic for therapeutic use. Leaves grown in a single locality often show great variations in activity, and it is true that Bohemian digitalis is often very potent. The toxic action of digitalis is simply an extension of the therapeutic action, and it would be as logical to complain of the toxicity of aconite or nux vomica as of that of digitalis.

"At the other extreme is the view that activity and quality must necessarily run parallel. Other things being equal, a drug of a given degree of activity is preferable to one showing but half of the activity; but the case with digitalis is not quite so simple, and it is far more important to have a drug of uniform activity than to have the most active drug that can be obtained. Furthermore, even a uniformly potent digitalis is not necessarily better than a uniform one of less potency, for digitalis contains (or yields) several therapeutic principles, and at least one substance, saponin, which is of minor toxicological importance;—of minor importance because it is present in the leaf only in traces. While all of the therapeutic principles of digitalis exert a more or less qualitatively similar action on the heart, they differ in certain essential side actions, and it does not necessarily

follow that the most active specimen of digitalis contains the largest proportion of the most desirable of these principles. Thus, true digitalin (of Schmiedeberg) is more actively emetic than digitoxin in proportion to its therapeutic activity (contrary to common teaching), and it may be that one specimen which is more active than another may contain the larger proportion of this relatively more active emetic, true digitalin, in which case the less active drug would be decidedly the more valuable.

"We need digitalis which will exert a maximum therapeutic action with a minimum of this undesired action, regardless of whether the drug is from wild or cultivated plants, and whether of the first or second year's growth, and regardless of the actual activity, even within certain limits, for one may administer a larger or smaller dose, provided the activity of the drug be known."

The study of digitalis from this point of view has received little or no attention, and Dr. Hatcher states that it is a field to which the pharmacist could well give some attention. The disagreeable features of this drug is its tendency toward nausea and vomiting, and while, to a certain extent, this is unavoidable, there is a possibility of minimizing it if one can only find out at what season the drug shows a minimum emetic action relative to its therapeutic effect.

While digitalis, like other vegetable drugs, will deteriorate when improperly stored, the extraordinary precautions and requirements of some of the European pharmacopœias are unnecessary; specimens of the whole or powdered leaves examined in the laboratory showed no evidence of deterioration after having been stored in the most ordinary manner in paper boxes, during periods varying from five to twenty-five years.

Speaking on the subject of digitalis from a pharmaceutical standpoint, this investigator emphasizes the necessity of a proper alcoholic content in its liquid preparations. Tinctures and fluidextracts should not only be made with a menstruum of 70 per cent. alcohol, but the finished preparation should actually contain that amount of alcohol; when this requirement is complied with deterioration does not take place in any important degree. Digitalis leaf and the preparations containing this amount of alcohol will retain their potency almost indefinitely without any serious loss if protected from air and sunlight.

Physicians who are inclined to be susceptible to the wiles of the detail man would do well to ponder these words: "Unfortunately,

with the appearance of every proprietary preparation bearing a new label and accompanied by the usual clinical support of its pretensions physicians run after it for a time, believing that the mystery of digitalis has been solved at last. The more observant usually return to the use of a good tincture, or the powdered leaf, when that is obtainable, and the wise pharmacist will stand ever ready to supply a dependable leaf, and a standardized tincture of his own manufacture."

It is generally believed that there is a difference in action between the infusion and tincture of this drug, but such is not the case; the tincture supposedly acting more on the heart and the infusion as a diuretic. Dr. Hatcher shows very clearly that a properly made infusion and tincture contains all of the therapeutically active principles of digitalis. The investigator also says it is easy to demonstrate that the marc left after preparing the tincture is inert by simply preparing an infusion from this marc and testing on a frog. The result is negative.—*The Druggists' Circular*, Sept., 1914, page 517.

J. K. T.

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## PHILADELPHIA COLLEGE OF PHARMACY.

### SEMI-ANNUAL MEETING.

The semi-annual meeting of the Philadelphia College of Pharmacy was held September 28, 1914, at 4 P.M., in the Library, the President, Howard B. French, presiding. Twenty-one members were present.

The minutes of the quarterly meeting held June 29th were read and approved.

The minutes of the Board of Trustees for the meetings held June 2d and 9th and July 12th were read by the Registrar and approved.

The Committee on nominations presented the list of names for vacancies in the Board of Trustees. The report was ordered entered and filed. The Committee on Membership reported for the year, making suggestions to increase the membership. The President announced the death of the following members since the last meeting: George J. Scattergood, William E. Lee, and Henry C. Eddy.

The President appointed as tellers to conduct the election for Trustees, Dr. Mitchell Bernstein and E. H. Hessler.

While the tellers were counting the ballots Professor Remington reported verbally for the delegates to the American Pharmaceutical Association meeting recently held at Detroit, Michigan. A full report of the meeting by M. I. Wilbert was published in the AMERICAN JOURNAL OF PHARMACY, September number, pages 464 to 471.

The tellers reported the results of the ballot for Trustees, that George M. Beringer, Joseph W. England, and C. Mahlon Kline had been elected for three years, and Samuel C. Henry for one year, whereupon the President declared the gentlemen named as duly elected.

The President appointed the Committee on Membership as follows: Charles H. La Wall, O. W. Osterlund, Richard H. Lackey, with the Treasurer and Secretary *ex-officio*.

Mr. Jacob S. Beetem reported that Mr. Frederick Gutekunst, a graduate of the College, had reached the age of eighty-three years, and he would suggest that the congratulations of the College be tendered Mr. Gutekunst. The suggestion was approved and the President appointed Professor La Wall to prepare a suitable minute, when the following was presented and unanimously adopted: "We, the members of the Philadelphia College of Pharmacy in semi-annual meeting assembled, do hereby extend the congratulations of the College to Mr. Frederick Gutekunst upon having successfully reached his eighty-third birthday. We are proud to feel that the great measure of his success has been partly due at least to the training which he received many years ago in our institution, and we hope that he may be spared to add many more laurels to his wreath of achievements."

It was also voted that the thanks of the College be tendered Mr. Gutekunst for the donation of photographs of some of the present and past officers and faculty of the College.

It was also voted that the thanks of the College be tendered Mr. George B. Evans for the gift of a number of bronze mortars and pestles and several other ornaments of value, collected by him in Europe.

C. A. WEIDEMANN, M.D.,  
*Recording Secretary.*

ABSTRACTS FROM THE MINUTES OF THE  
BOARD OF TRUSTEES.

*June 2nd, 1914.*—Sixteen members present. Committee on announcement reported the catalogue number of the Bulletin in press. A sketch of the new certificate was adopted, and the Registrar was directed to place an order at the price agreed upon. Mr. Campbell, for the Special Committee on N. A. R. D. exhibit, reported having arranged for a booth at their Convention, and explained the nature of the exhibit. Mr. George B. Evans kindly agreed to assist in making the exhibit attractive, and also recommended that the exhibit be made.

*June 9th, 1914.*—Adjourned meeting. Sixteen members present. Committee on Examinations presented the names of those recommended for the degree of Doctor in Pharmacy (P.D.). A teller was appointed and the ballot was then taken and reported clear, and the Chair then declared those named elected to receive the degree of Doctor in Pharmacy. The names of those recommended for the degree of Pharmaceutical Chemist (P.C.) was then read, and, a ballot being taken and reported clear, the Chair declared them elected to receive the degree of Pharmaceutical Chemist. The committee reported that Professors Sadtler and Moerk had recommended that a Certificate of Proficiency in Chemistry be awarded to Harry C. Karns, P.D. The recommendation was approved. The committee also presented a communication from Professor Roddy giving the names of those entitled to receive a Certificate in Bacteriology, and recommended that they be granted. It was so ordered. The committee also presented the name of Paul Donmoyer, Class of 1907, for a Certificate in Bacteriology, as recommended by Professor Kraemer. On motion it was ordered that the certificate be granted and that others who had taken the course under Professor Kraemer and had passed the required examination should be granted certificates and Professor Kraemer be authorized to sign same. The names of those who had won prizes were then read, and the Chair appointed those who were to present same at the Commencement exercises. Committee on Commencement reported that Governor Tener had consented to address the Graduating Class. Mr. Rumsey moved that a vote of thanks be conveyed to those assisting in the Commencement exercises. It was so ordered.

*July 22nd, 1914.*—A special meeting of the Board was held, in answer to the call of three members, to take action on the death of William E. Lee, a member of the Board. Eleven members were present, and regrets at not being able to be present were received from seven members. Remarks appropriate to the life and character of Mr. Lee were made by Messrs. Boring, Campbell, England, Moerk, Poley, and Weidemann. Mr. Mulford moved that a committee of three be appointed to draft resolutions to be entered on the minutes and an engrossed copy sent to the family. Being so ordered, the Chair appointed Messrs. Mulford, England, and Campbell as the committee. It was suggested that flowers be sent to the house on the day of the funeral. This being considered a special tribute, the members personally paid the expense.

## DEPARTMENT OF AGRICULTURE DISCUSSES OBJECTIONABLE LABELLING FOR MEDICINAL PREPARATIONS.

In answer to many inquiries as to proper labelling for medicinal preparations to comply with the Food and Drugs Act as amended, the Department of Agriculture, through the Bureau of Chemistry, has issued the following suggestions to makers and proprietors of medicinal preparations:

1. *Claims of Therapeutic Effects.*—A preparation cannot be properly designated as a specific, cure, remedy, or recommended as infallible, sure, certain, reliable or invaluable, or bear other promises of benefit, unless the product can, as a matter of fact, be depended upon to produce the results claimed for it. Before making any such claim the responsible party should carefully consider whether the proposed representations are strictly in harmony with the facts; in other words, whether the medicine, in the light of its composition, is actually capable of fulfilling the promises made for it. For instance, if the broad representation that the product is a remedy for certain diseases is made, as, for example, by the use of the word "remedy" in the name of the preparation, the article should actually be a remedy for the affections named upon the label under all conditions, irrespective of kind and cause.

2. *Indirect Statements.*—Not only are direct statements and rep-

representations of a misleading character objectionable, but any suggestion, hint, or insinuation, direct or indirect, or design or device that may tend to convey a misleading impression, should be avoided. This applies, for example, to such statements as "has been widely recommended for," followed by unwarranted therapeutic claims.

3. *Indefinite and Sweeping Terms.*—Representations that are unwarranted on account of indefiniteness of a general sweeping character should be avoided. For example, the statement that a preparation is "for kidney troubles" conveys the impression that the product is useful in the treatment of kidney affections generally. Such a representation is misleading and deceptive unless the medicine in question is actually useful in all of these affections. For this reason it is usually best to avoid terms covering a number of ailments, such as "skin diseases, kidney, liver, and bladder affections," etc. Rheumatism, dyspepsia, eczema, and the names of many other affections are more or less comprehensive, and their use under some circumstances would be objectionable. For example, a medicine should not be recommended for rheumatism unless it is capable of fulfilling the claims and representations made for it in all kinds of rheumatism. To represent that a medicine is useful for rheumatism, when as a matter of fact it is useful in only one form of rheumatism, would be misleading, such statements as "for some diseases of the kidney and liver," "for many forms of rheumatism," are objectionable, on account of indefiniteness.

Names like "heart remedy," "kidney pills," "blood purifier," "nerve tonic," "bone liniment," "lung balm," and other terms involving the names of parts of the body are objectionable for similar reasons.

4. *Testimonials.*—Testimonials, aside from the personal aspect given them by their letter form, hold out a general representation to the public for which the party doing the labelling is held to be responsible. The fact that a testimonial is genuine and honestly represents the opinion of the person writing it does not justify its use if it creates a misleading impression with regard to the results which the medicine will produce.

No statement relative to the therapeutic effects of medicinal products should be made in the form of a "testimonial" which would be regarded as unwarranted if made as a direct statement of the manufacturer.



5. *Refund Guarantee.*—Statements on the labels of drugs guaranteeing them to cure certain diseases or money refunded may be so worded as to be false and fraudulent and to constitute misbranding. Misrepresentations of this kind are not justified by the fact that the purchase price of the article is actually refunded as promised.

WASHINGTON, D. C.

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## GINSENG GROWERS MAY FIND GOLDENSEAL AN ADMIRABLE SIDE CROP.

HOWEVER, MARKET FOR THIS NATIVE DRUG PLANT IS LIMITED, LABOR COSTS ARE HIGH, AND SPECIAL CARE IN CULTIVATION IS NECESSARY.

Goldenseal is a native drug plant of admitted commercial value, which is rapidly becoming scarce, and farmers who have had experience with ginseng may find in goldenseal an admirable side or succession crop. This is the opinion of one of the U. S. Department of Agriculture's drug-plant specialists, whose pamphlet, "Goldenseal Under Cultivation," has just been issued as Farmers' Bulletin 613. Goldenseal, known to the pharmacist and physician as *hydrastis*, is native to open woodland where there is ample shade, good natural drainage, and an abundance of leaf mold. It is most abundantly found in Ohio, Indiana, West Virginia, and Kentucky, though it grows west to Minnesota, south to Georgia, and in southern New York. It is not grown in Europe on a commercial scale, and the United States exports quantities of this drug to Germany.

In general, drug plants are difficult to grow, labor costs are high, and the market is limited. These drawbacks are true to goldenseal but ginseng growers who are already equipped for the culture of exacting woodland plants, but whose ginseng crops have been attacked by pests and diseases, should meet with some success with goldenseal. The latter requires essentially the same conditions as the other crop, but is easier to grow, being far less subject to disease and attacks from mice.

### STEADY ADVANCE IN MARKET PRICE.

There began to be a commercial demand for goldenseal about 1860, and since then its use has become world-wide, although most of it is consumed in this country. It is valued solely for its remedial

properties, and was commonly used by Indians and early settlers as a remedy for sore mouth and inflamed eyes; also as a bitter tonic in stomach and liver troubles.

Until about the year 1880 the prices paid for crude goldenseal rarely ranged over 8 to 12 cents a pound, these prices, as a matter of course, being based on the actual cost of collecting and curing the material where it was abundant. In 1890, however, the approaching scarcity of the root was manifested by rising prices, and at the close of the next decade the cost had advanced to an average of 58 cents a pound. Early in 1904 the price passed the dollar mark, the year closing with wholesale quotations varying from \$1.35 to \$1.50.

With the exception of slight fluctuations in 1912, which were apparently the result of overcollection, there has been a steady advance in the price of the dried root, both wild and cultivated. The prices paid to growers and collectors of goldenseal for the last three years have ranged from \$3 to \$4.25 a pound, and these prices are thought to be a fair basis of profit in goldenseal culture, even after taking into consideration the rather exacting requirements of the plant and its relatively slow progress toward commercial maturity.

#### NOT AN EASY CROP TO GROW.

It costs about \$1500 an acre, exclusive of the value of the land, to start a goldenseal plantation. This includes the average cost for propagating material, but makes no provision for irrigation during dry weather. Of course, special conditions, such as local cost of labor, lumber, and fertilizers, will influence this estimate. This outlay might well discourage those who wish to cultivate the plant on a large scale, but small home and experimental plantings may usually be started at a very small cost. In any case the plan requires special care and suitable conditions at all stages of its development.

Goldenseal takes considerable time to develop. If it is grown from seed under favorable conditions it only reaches its best development for market after about five years. If it is grown from root buds or by division of the rootstock, it reaches its best development in three or four years. Successful growers have outputs of about 2000 pounds of dried root per acre after five years from seed. Better showings might be made by well-equipped small growers.

A market for goldenseal is found with the crude drug dealers and manufacturing druggists in most large cities. This root is also handled on commission and is readily purchased by fur buyers and traders in miscellaneous forest products. The estimated annual consumption, however, is only 100 tons, and as only about 500 acres would be needed to produce that amount, overproduction would be easy. Prospective planters must bear this in mind, as well as the fact that this estimate makes no allowance for the wild supply of the root, which is still a factor, although rapidly decreasing.

Ginseng growers will be interested in the new bulletin on goldenseal. It goes into great detail regarding methods of cultivation, and may be had free on application to the Division of Publications, U. S. Department of Agriculture, Washington, D. C.

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## THE POISONOUS NATURE OF THE STINGING HAIRS OF *JATROPHA URENS*<sup>1</sup>

*Jatropha urens* is one of the most abundant Euphorbiaceous plants growing in or around the savannas of the Pacific coast of Central America. Its spread is favored by the fact that the cattle avoid it, and because it is not kept down by the too indolent owners of the pastures. Everywhere it has the reputation of being extremely dangerous, on account of its poisonous effects.

The plant is easily recognized: It is herbaceous, 0.5 to 1.5 meter high, regularly ramified, with large, palmatilobate leaves, white flowers and small, 3-celled capsules. All parts, trunk, leaves, flowers and fruits are covered with long, hard and glossy, stinging hairs, which protect the plant as barbed wire protects the fortifications of to-day. It would seem as if the remarkable glossiness of the stinging hairs might warn the curious against approaching or touching. As a matter of fact, the animals, either by instinct or on account of the wisdom acquired through some previous experience, avoid contact with it.

The vernacular name of *Jatropha urens* is "ortiga" or "ortiga brava" (nettle) in Panama, and other parts of Central America, indicating somewhat its noxious effects. Sometimes it is also called "chichicaste."

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<sup>1</sup> *Science*, October 23, 1914, p. 609.

The stinging hairs of *Jatropha urens* show the same structure as those of the common nettle (*Urticacæ*), though the two plants belong to different families. The poison is produced by a cell of the epidermis which, during the growth, swells up, forming a goblet-shaped bulb, set into the surrounding tissue. The hair then represents a long tube, the walls of which have incrustations of silicic acid in the upper part and are calcified in the lower parts, so that they are very brittle and break at the lightest touch. Near the top this cell expands a little, in the form of a miniature hat with very thin walls, so that when touched, it breaks in an oblique direction, forming the point of a cannula, which enters the skin of animal or man. At the same time the poisonous liquid of the cell is discharged into the wound, and produces instantly a local inflammation. The mechanism is, in fact, the same as that of the poison fang of the snakes, and it is also similar to the cannula of the surgeon.

To estimate the formidable effects of the hair and the intensity of its poisonous liquids, it has been calculated that about 10,000 hairs of the common nettle may produce one drop of poison (0.05 c.cm.). As in the case I am going to mention, about 10 hairs of the *Jatropha* were broken. It may be calculated on the same basis that about 0.00005 c.cm. of poison entered the wound. This is, however, a low estimate, because the hairs of our plant and their inner cavity are larger than those of the common nettle and the amount of poison introduced into the system in the following occurrence was probably much larger than it would have been in the case of an equal contact with *Urtica urens*.

On an excursion along the San Felix River, in eastern Chiriqui, with Dr. MacDonald, geologist of the Canal Commission, the writer became acquainted with *Jatropha urens* by unavoidable contact with a single specimen of the plant. All at once he felt an intense burning on the left hand, where about 10 of the stinging hairs had entered pretty deep into the skin. The inflammation produced by this touch was very similar to that produced by nettles, but the pain soon increased, the whole hand began to swell and inside of half an hour had assumed a monstrous shape. Then the arm commenced to swell also, the right hand and arm, without having been inoculated, yet showed the same abnormal symptoms, and a very strong itching sensation was felt all over the upper part of the body. At about the same time parts of the face, around the eyes and nose, swelled

considerably. The itching sensation rapidly spread over the abdomen and the lower extremities and red pimples appeared everywhere. In less than an hour the poison had extended over the whole surface of the body, and its entrance into the blood current was indicated by the corresponding physiological reaction of the interior organs. The palpitation of the heart became extremely accelerated and the mind was soon overcome by an agonizing depression. The respiration seemed to be delayed as if under a great pressure, cold sweat broke out, and the patient gave way altogether, remaining unconscious for more than an hour, except for feverish dreams. After coming back to his senses, he had several fits of copious vomiting, from which it may be surmised that the poison was slowly eliminated from the organism. The weakness, however, remained for several days.

A case of such extreme effects, which might have killed a man of less strength than the writer, has never been recorded, as far as the literature on the subject shows. Undoubtedly the intensity of the intoxication was due to the rather strong contact with the plant, which caused a considerable amount of poison to be introduced into the blood circulation.

Many other tropical plants, among them some *Urticaceæ* and *Loasaceæ*, have such deadly stinging hairs, the poison of which is active enough to kill a man, even in a relatively small dose. The only way of allaying its effects would be to neutralize or precipitate it by means of a prompt application of chloride of lime, ammonia or sodium permanganate.

OTTO LUTZ

INSTITUTO NACIONAL DE PANAMA,  
PANAMA, R. DE P.

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## UNITED STATES CHAMBER OF COMMERCE TO STUDY FOOD AND DRUG QUESTIONS

The Chamber of Commerce of the United States of America, a body composed of representatives from about 600 local boards of trade, chambers of commerce, and trade associations, widely distributed throughout the United States, has taken up the study of the subject of uniform food and drug regulation. For this purpose a special committee was appointed in July, and its first meeting was

held at the headquarters of the Chamber in Washington, October 8th. The committee is composed of Willoughby M. McCormick, of Baltimore; A. J. Porter, of Niagara Falls; John A. Green, of Cleveland; B. L. Murray, of New York, and Theodore F. Whitmarsh, of New York. Mr. McCormick, the chairman, is a member of the Board of Directors of the Chamber of Commerce of the United States, and the head of the firm of McCormick & Co., manufacturers of extracts and drugs and importers of spices and teas; Mr. Porter is president of the Shredded Wheat Company; Mr. Green is secretary of the National Association of Retail Grocers; Mr. Murray is chemist to Merck & Co.; and Mr. Whitmarsh is vice-president of Francis H. Leggett & Co.

The position taken by the committee on the meaning of uniformity is interesting and will repay close examination. Its views are not confined to a limited horizon but are intended to grasp the broader and wider fields. Its efforts will be confined to no organization or class of people. It hopes to cover in its endeavors the position of the wholesaler, the retailer, the consumer, the manufacturer, the official, and all others concerned in the production, handling and consumption of food and drugs. But only the broad, general questions of national character will be considered. After a lengthy discussion the committee at its meeting, by unanimous vote of all present, adopted the following regarding uniformity:

Uniformity, as the committee would define it, involves the highest degree of efficiency in food and drug control which it is possible to have prevail universally and equally in every part of the nation. The Federal, State, and municipal laws and their regulations would, if perfect uniformity were attainable, reach the level of full and complete efficiency, and thereby afford equal protection and a uniform standard of living for all the people. Uniformity accomplished, places merit and the general public interest over local political or geographical divisions. This committee will, therefore, direct its efforts and consideration toward the accomplishment of uniformity. The committee cannot but feel impressed with the magnitude, the importance, and the seriousness of its work. It cannot but feel the need for the closest study of the subject. And, again, the committee cannot but feel the necessity for the fullest and most cordial coöperation between itself and the officials and all others concerned. The committee will, of necessity, act deliberately and slowly, making certain of each step, considering only the important problems of a national character.

# THE AMERICAN JOURNAL OF PHARMACY

DECEMBER, 1914

## BELLADONNA AND HYOSCYAMUS.<sup>1</sup>

By EDWIN L. NEWCOMB, College of Pharmacy, University of Minnesota.

### PART I.—CULTIVATION EXPERIMENTS.

*Atropa Belladonna* and various species of *Hyoscyamus* have been carefully studied for some time and descriptions have been prepared by chemical and botanical workers. Recently some additional observations have been made and work done by the writer, the results of which seem of sufficient importance to present.

Seeds of *Atropa Belladonna* L. and of various species and varieties of *Hyoscyamus* were secured from various sources and plants propagated from them used for the work. In the securing of seeds of *H. niger* L. and of *H. albus* L. it was learned that other botanical names were sometimes applied to these plants and that some confusion exists in the use of the various synonyms. According to the Index Kewensis, the following named plants are identical with *Hyoscyamus niger* L.: *H. agrestis* Kit., *H. auriculatus* Tenore, *H. bohemicus* F. W. Schmidt, *H. lethalis* Salisb., *H. officinarum* Crantz, *H. pallidus* Waldstand Kit., *H. persicus* Boiss and Buhse, *H. pictus* Roth., *H. syspirensis* C. Koch, *H. verviensis* Lej., and *H. vulgaris* Neck; and the following identical with *Hyoscyamus albus* L.: *H. aureus* All., *H. canariensis* Ker-gawl., *H. Clusii* G. Don., *H. luridus* Salisb., *H. minor* Mill., *H. major* Mill., and *H. varians* Vis in Flora. Unquestionably there is a wide range of variation in *H. niger* L. and *H. albus* L., and, while some of the above synonyms probably arose from the discovery and naming of the plants by independent workers at about the same time, still others represent

<sup>1</sup> Presented to the Philadelphia College of Pharmacy for the degree of Master in Pharmacy in course.

variations of but a fraction of a unit character from the type. Then again the name *H. agrestis* Kit. has been applied to the specific annual form of *H. niger* L. Many of these early specific names are still more or less in use, and, while one may secure seeds from a number, the resulting plants conform to type specimens of *H. niger* L., *H. albus* L., or to hybrids. Furthermore, it appears to be quite impossible at the present time to secure seeds of *Hyoscyamus* which represent pure races from any of the various seed dealers.

#### CULTURE AND WINTERING.

The seeds of *H. niger* L. biennial germinate in about the same length of time after being planted as do the seeds of *Atropa Belladonna*, most of the seeds requiring from four to six weeks to come up, while a few may require much longer. The seeds of *H. niger* L. annual and *H. albus* L. germinate quite evenly in from eight to ten days. With proper care the plants make a very rapid growth. No particular difficulty was experienced in the cultivation of several hundred of each species. *Hyoscyamus*, however, requires rather more attention than most plants in connection with transplanting, spraying, watering, hoeing, etc.

The biennial plants forming the basis of the work reported in this paper were protected during the winters by the following methods: After the first hard freeze coarse straw manure about a foot deep was placed over the garden plots of *Atropa Belladonna* and *H. niger*, the roots of a second lot dug up and buried in a protected location, while a third lot of each were potted and stored in a cold-house. The *Belladonna* plants all survived the first winter except those left out in the garden plots. During the second winter (1912-13) all *Belladonna* plants survived. The potted plants of *Hyoscyamus* were the only *Hyoscyamus* plants that survived both winters. The lowest outside temperature during the first winter (1911-12), as determined by an accurately recording thermometer placed in the garden, was  $-33^{\circ}$  F., and for the second winter  $-22^{\circ}$  F.

I have subjected the various species and varieties of *Hyoscyamus* plants and *Belladonna* plants that I have grown during the past three summers to varying conditions in order to learn more concerning their exact nature and habits. The increased use of drugs from cultivated plants makes such studies of prime importance, and, while



ecologic and physiologic investigations have been carried out with a number of medicinal plants, for the most part these studies have not been made with the object in view of securing vegetable drugs of uniform maximum medicinal values.

#### THE ALTERNATING ANNUAL AND BIENNIAL HABIT.

In connection with the cultivation of *Hyoscyamus* I have given some attention to the constancy of the various forms under observa-



FIG. 1.—*Hyoscyamus niger*, biennial. Portion of a plot showing rosette character of the leaves and their long petioles.

tion, to determine the presence or absence of the alternating annual and biennial habit. Before giving the results of my own experiments along this line I will briefly discuss the phenomenon.

De Vries states that in plants which possess the alternating annual and biennial habit the biennial species which presents the character of occurring partly in annual and partly in biennial specimens must possess the capacity of growing as annuals in a semi-latent condition, and that this capacity does not seem to be universal, but to be

confined to particular races. De Vries presents experimental evidence to prove that biennial species which possess this semi-latent capacity are, in becoming annuals, largely influenced by external factors. A large number of plants will become annual if the seeds germinate early or biennial if their seeds germinate late; here the stimulus of the spring frost or cool weather is in some cases a factor which causes annuals or bolting, as in the sugar beet. In addition, many plants possess an inherited variability to be either annuals or biennials.



FIG. 2.—Flowering branches of *Hyoscyamus niger*, annual.

In summing up experiments on *Oenothera*, De Vries shows that "biennial species which possess in a semi-latent state the capacity to produce annual specimens can be induced to manifest this anomaly to a much greater extent by supplying them with more food. Crowding of plants, shading, lack of manure, or cultivation on sand favors the production of biennials; but the more space, light, and nourishment in the soil there is at the disposal of the individual plants the greater will be the number of those which will produce stems, flower, and ripen their seed the first summer." Continued selection fails to

fix the biennial races and to free them of annual species or to free the annual races of biennial individuals.

Holmes, in considering the occurrence of annual plants in the biennial henbane fields of England, states that "the seeds of the capsules last formed are often deficient in vitality and the plants produced from them flower the first year, hence the occurrence of annual plants among the biennial."

In discussing *Oenothera Lamarkiana* (a plant which possesses the semi-latent alternating annual and biennial habit) De Vries says that he found about the same number of annual and biennial individuals from the upper and lower fruits of the same spike, and, furthermore, he draws the conclusion from his work on *Trifolium pratense quinquefolium* that the better the seeds are fed on the plant the greater is the development of the anomaly on the individuals produced by them. Poor seeds give rise to atavists, good ones to extreme variants.

If we accept the quite general belief that perennial and biennial plants are of older origin than annual plants, then we cannot consider the annual henbane as atavistic. On the choice of seeds in selection De Vries states, after weighing the evidence of a large number of workers, as well as his own, that "when we are dealing with semi-latent or, in general, with highly variable characters a selection of seeds either by their size and weight or by their place of origin on the plant is to be recommended in many cases, and the general rule seems to be that the place of origin of the best seeds will also be that of the desired variants." There are some cases in which this rule does not apply, as in *Trifolium incarnatum*. In this latter plant De Vries found that the reverse of the general rule held good, and the result of this work was so strikingly different from all other that he leaves the explanation an open question. This occurrence of the annual form of *Hyoscyamus niger* in English henbane fields is probably due to hybridization (which will be discussed later in this paper) rather than to semi-latent characters in the biennial *Hyoscyamus*.

I will now describe my own experimental attempts to bring out semi-latent characters in *Hyoscyamus*. All plants grown outside were cultivated in the Medicinal Plant Garden, College of Pharmacy, University of Minnesota.

## EXPERIMENTAL PLANTING, 1911.

My first planting, on February 17th, consisted of a sample of seed labeled *Hyoscyamus niger* and purchased as the biennial form. The germination of this sample was very poor, only four seed giving rise to plants. On March 17th three of these plants continued to grow and were transferred from the seed-pan to individual pots. Each plant developed a rosette of basal leaves and was typical of the biennial henbane. All three plants died later in the season, due

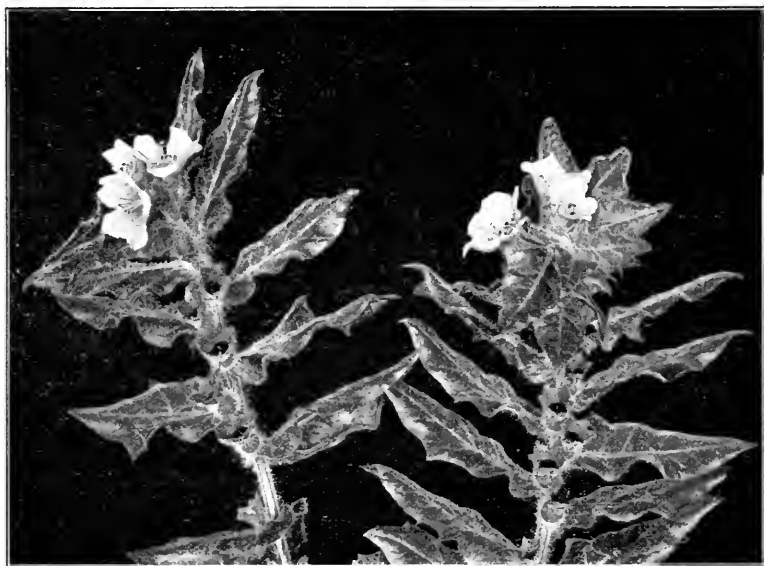


FIG. 3.—Flowering branches of *Hyoscyamus albus*.

to lack of attention and a proper understanding of how the plants should be cared for.

A second planting of the seed referred to above was made on March 17th, and in twenty-four days a few seed had germinated. Fifteen plants were secured from this second planting, and these were transferred to a sandy loam plot in the medicinal plant garden as soon as danger of frost was over. The soil or other conditions seemed unsuited for the plants, and they made very little growth after being planted out. A long hot spell resulted in all plants dying. Each plant produced a weak rosette of basal leaves, but there was no tendency for the development of a shoot.

The second sample experimented with in 1911 consisted of a lot of seed purchased as the drug *Hyoscyamii Semen*. Some of these seed were sown on February 22nd and a second lot on March 26th. Both plantings required about three weeks to germinate. From these plantings seventy plants were secured and transferred to flats containing good, rich potting soil. The plants all made rapid growth and began to send up flowering shoots in about three weeks. The characteristic rosette of basal leaves of the biennial plant was not present in a single specimen. All of the plants flowered before the weather was suitable for outside planting, and, although the plants were small, they represented typical annual *Hyoscyamus niger*.

On April 26th seed of *Hyoscyamus niger*, *H. albus*, and *H. pictus* were sown in cold frames. These all germinated in from eight to ten days, and *H. albus* coming up first. The soil in the seed beds was very light and sandy. No fertilizer whatever was applied. All of these plants were allowed to remain in the cold frames, the sash being permanently removed as soon as danger of frost was over. The plants were crowded in rows, and the rows were close together. Other larger growing plants around the cold frames soon placed the *Hyoscyamus* in quite dense shade. The conditions affecting the growth of the plants throughout the season were such, that had semi-latent biennial characters been present in any of the plants one would have looked for a large number of biennial forms. The result of the experiment, however, was that every one of about two hundred plants in each row sent up the flower stalk, produced flowers, and fruited.

#### EXPERIMENTAL PLANTING, 1912.

The first planting in 1912 was done on March 2nd, and consisted of three lots of seed freshly imported from Germany and labeled as *Hyoscyamus niger*, *H. albus*, and *H. pictus*. I secured a good, even germination from each of these trials in two weeks' time. About seventy-five plants of each lot were transferred to flats the 1st of April, and to three-inch pots May 14th. Two weeks later they were planted out in the open garden, being placed in plots of two different kinds of soil. One-half of the three species were placed in a very light sandy loam and the other half in soil consisting of light sandy loam mixed with about equal parts of rich, well-rotted peat and other humus. All of the plants made a good, continual growth from the time the seeds germinated until maturity,

and all plants produced flower stalks, flowers, and fruits without showing any signs of the biennial character.

The second planting for this season was made on March 14th, and consisted of a sample of seed labeled Henbane and purchased for the biennial form. This sample germinated unevenly, but a fairly large proportion of the seed had started to grow by April 10th. About fifty of the plants grown from this lot of seed were placed in flats on April 24th, and the latter part of May they were transferred to the open, twenty-five of the plants being placed in a sandy loam mixed with an equal amount of peat humus, and the remaining twenty-five in a plot the soil of which consisted of about one foot of clean sandy loam underlaid with cinders and sand. All of the plants made a good growth and were all characterized by the numerous typical basal leaves of the biennial henbane. The plants were watered by city water with a hose when rain was not sufficient. Most of the plants in the sand underlaid with cinders died during the latter part of the summer, when it was exceedingly hot. Those plants in the richer soil, however, continued to grow luxuriantly, and by fall many of them were two feet across. None of the plants under either condition showed any sign of producing flower stalks.

The third planting, on March 21st, 1912, consisted of a fresh sample of seed labeled *Hyoscyamus niger* and obtained from Germany. In this planting germination was very poor, only eighteen plants being obtained, and the seed which produced these few plants required from three to four weeks to germinate. All of these plants grew rapidly, produced flowers and fruits, but did not show the biennial habit in any respect, although they were not grown under the most favorable conditions.

#### EXPERIMENTAL PLANTING, 1913.

All planting of *Hyoscyamus* seed in the spring of 1913 was done on February 7th, at which time five different lots of seed were sown.

Lot number one and lot number two were each bought for *Hyoscyamus niger*, biennial. The seed of these two lots germinated quite evenly, requiring from four to five weeks to come up. Twenty plants from each lot were placed in separate flats with rich potting soil on March 20th, where they continued to grow for about three

weeks. The plants were then put into three-inch pots, where they were held until transferred to the garden, early in May. All of the plants were placed in a plot in which the soil was composed of very rich garden loam. A late spring frost injured many of the plants, but they soon recovered and made a vigorous growth throughout the summer. Each plant produced a large rosette of basal leaves, but not a single plant showed any tendency to develop the flowering stalk.

The third, fourth, and fifth lots of seed sown in the spring of



FIG. 4.—Flowers of *Hyoscyamus niger*, annual.

1913 were freshly imported from Germany and were labeled respectively as follows: *Hyoscyamus niger*, *H. albus*, and *H. pictus*. In each lot germination took place in about ten days. Seventy-five to ninety plants from each lot were transferred to flats as soon as the second pair of leaves were well formed. When the plants became crowded in the flats they were placed into three-inch pots. The plants grew rapidly and many had produced flowers by the time they were planted in the garden, which was early in May. Most of the plants were placed in pots in which the soil was quite rich, and

within a short time every plant had produced a flower stalk, flowers, and fruit. The plants continued flowering throughout the early summer and then died.

The results of these experiments, in so far as semi-latent characters are concerned, may be summarized in a very few lines. Altogether over twelve hundred plants were grown, and these were subjected to a number of varying conditions, with the result that not a single plant showed any tendency to change from the annual to the biennial form or from the biennial to the annual form. While these experiments are probably not conclusive, they indicate that pure races probably exist of the annual and biennial forms of *Hyoscyamus*.

#### HYBRIDIZATION.

The work which I have thus far done has not included any experimental crossing of the different species and varieties of *Hyoscyamus*, but in the attempt to secure pure species and races for later work some observations have been made which seem worthy of mention. Throughout the cultivation of *Hyoscyamus* it has been noted that the amount of pigment in the flowers was exceedingly variable. In *Hyoscyamus* there are two distinct color units, which may be termed physiologic units. The first of these is represented by anthocyanin, to which is due the dark coloring of the veins of *Hyoscyamus niger*, and the second is a yellow element. During the past season, when several hundred plants of *Hyoscyamus*, grown from commercial seed supplies, were under cultivation, I arranged twenty plants, each with a slightly varying amount of color, in such an order as to represent at the one end a typical specimen of *H. niger* with the maximum amount of anthocyanin, while at the other end of the row a plant difficult, if not impossible, to distinguish from typical *H. albus*. This condition appears to be explained by the somewhat extended experiments on the hybridization of different species and forms of *Hyoscyamus* by De Vries and by C. Correns. From the results of these experiments it is shown that *H. niger* var. annual readily crosses with *H. albus*, and that the anthocyanin is a dominant character. Crosses between *H. niger* annual and *H. niger* biennial have also been made, and in such crosses the biennial form appears to dominate. The pedigree of the crosses conforms to the laws of Mendel, even when the experiments have been carried into the third generation.



Pollination in *Hyoscyamus* plants not under experimental control takes place partly by means of insects carrying pollen from the flowers of one lot of plants to the flowers of other plants which may be of a different variety or form. This gives rise to vicinists, and hence seed supplies from field-grown or wild plants collected where several forms are growing together will not infrequently produce hybrids rather than pure species or varieties. And for the same reason commercial seed supplies, unless obtained from plants grown under control or from plants grown in isolated districts, will not

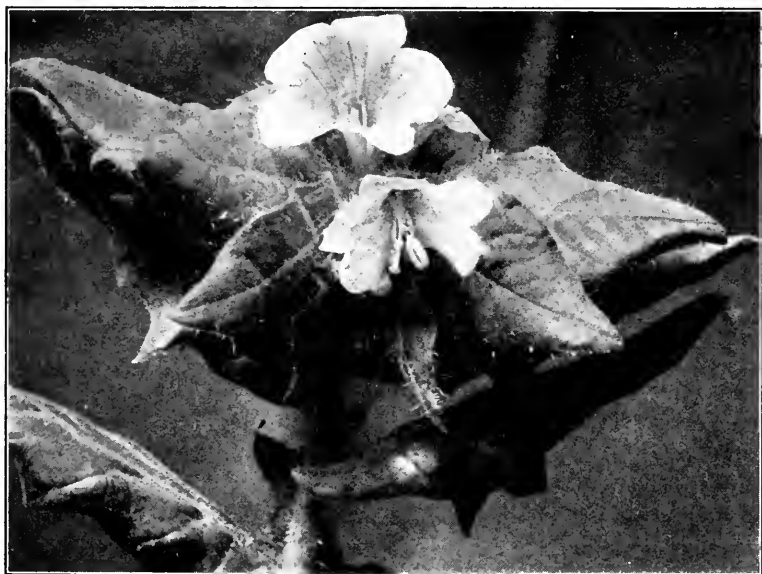


FIG. 5.—Flowers of *Hyoscyamus albus*.

always yield pure races. Furthermore, it should be pointed out that *H. albus* is probably not an elementary species, but rather a retrograde variety of *H. niger*, in which the unit character anthocyanin is more or less latent. This difference between elementary species and certain systematic species has been fully discussed by De Vries, and the importance of a physiological classification based upon physiological units should not be underestimated by those engaged in medicinal plant breeding. To illustrate the difference between an elementary species and a systematic species or variety, De Vries

calls attention to *Datura Tatula* and *Datura Stramonium*, in which every analogy points to the blue as the older and the white as the younger form or retrograde variety. *Atropa Belladonna lutea* is another example of a plant where the physiologic unit anthocyanin is lost or latent, and this plant we consider as a variety of *Atropa Belladonna*. The actual proof of the relationship between elementary species and varieties is, of course, rarely to be obtained.

From this brief discussion on hybridization and the principles involved it seems most probable that the occasional annual forms of *Hyoscyamus* in the biennial henbane fields of England is due to natural hybridization.

At this time I desire to call attention, first, to the importance of the determination of the exact nature of the plant,—i.e., whether it represents an elementary species, a variety, a hybrid, a constant or an inconstant form; and, second, to the need for close and critical study of the medicinally active constituents as physiologic units. Following this, selection and hybridization for the purpose of producing better drugs may proceed along scientific lines and interchanges or combinations of desired unit-characters formed.

(To be continued.)

## STANDARDIZATION OF COMMERCIAL PAPAIN.

By F. W. HEYL, C. R. CARYL, and J. F. STALEY.

The term "papain" is supposed to describe an especially prepared product containing the enzymatic constituents in greater proportion, and hence having a higher digestive activity, than the crude juice. Thus, in Merck's "Index" papain is described as having a digestive power on blood fibrin of 1 : 200, whereas the proteolytic activity of the dried juice is only 1 : 80. For the latter determination no method of standardization is suggested, although the fibrin test is probably understood.

The fibrin test is decidedly awkward and inelegant. Furthermore, there are some important disagreements as to the conditions under which the test should be carried out. In Hager's "Handbuch der Pharmaceutischen Praxis" this test<sup>1</sup> is described as being carried out in a medium made slightly alkaline with sodium

<sup>1</sup>Band 1, 640.

hydroxide, and that the fibrin is acted on for from four to five hours at 45° to 50° C. It is there further stated, however, that the products of several different manufacturers vary as to their activity in acid and alkaline medium respectively. Thus it is stated that the preparations of E. Merck and of Gehe & Co. acted best in alkaline medium, while, on the other hand, those of Boehringer and of Finkler were active in acid solution.

The fibrin test has been little used in this country because of the doubtfulness of the method and because of the experimental difficulties involved in carrying it out. During recent years our literature contains several contributions dealing with assay methods which are more serviceable than the assay by means of fibrin.

However, during the period in which these newer methods were being evolved the commercial product has been adulterated to a shameful extent, and the terms "papain" and "pawpaw juice" are not now characteristic of two different products. Indeed, papain now really signifies dried pawpaw juice. We have found no products on the market having a higher digestive strength than has dried pawpaw juice, although the terms "papain," "purified papain," "concentrated active principle," etc., were used in describing some of the various products. Some of these were offered for greatly advanced prices, in one case the price per pound being almost \$10. Official recognition of this product, as well as a method for standardization, is very desirable.

Among the newer methods, we have one described by Graber.<sup>2</sup> This method is that of allowing 10 grammes of properly prepared round steak to stand with 0.325 gramme of papain in the presence of 85 c.c. of 0.3 per cent. hydrochloric acid at 52° C. for six hours. The undigested portion should not measure more than 2 c.c. in a graduated settling tube. The proteolytic activity then, under these conditions, is 1 : 30. Graber describes the results obtained by this method in studying the activity of pawpaw juice, but not of commercial papain. He found the proteolytic activity on steak to be greatest in a 0.3 per cent. hydrochloric acid medium.

Horace North<sup>3</sup> examined twelve samples of commercial papain, six of which proved by his method to be inactive. The experimental values showing the comparative activity of the six genuine samples

<sup>2</sup> *Jour. Ind. and Eng. Chem.*, 3, 919 (1911).

<sup>3</sup> Report of Lehn & Fink's Analytical Department, 1910-1912, p. 66.

are not given. North does not state whether or not the active samples contained any starch, although this adulterant was noted by him in the valueless samples. North used the test which is official for pepsin. A residue of 36 c.c. is obtained from ten grammes of coagulated egg-albumin. In the assay 0.05 gramme of papain is allowed to act on ten grammes of albumin. After digestion with a good sample of papain a residue of only 6 c.c. remains. In his calculations North allows for a blank of 1 c.c., exactly as in the U. S. P. method for pepsin. The proteolytic activity then was calculated as follows: There remained 6-1 or 5 c.c. of albumin after the digestion, hence 30 c.c. was digested. The proteolytic ratio, therefore, was  $\frac{30}{5}$  or 6. If the papain had digested the 10 grammes completely, the proteolytic ratio would have been 1 : 200. In this case, then, the ratio was 1 : 171. This ratio, like the one given by Graber, is for digestion in an acid medium.

Rippetoe<sup>4</sup> assayed papain by using 40 c.c. of a 0.1 per cent. sodium hydroxide solution, 10 grammes of egg-albumin (prepared as directed in the U. S. P.), and by carrying out the digestion at 52° C. for six hours. The quantity of papain used was 0.1 or 0.2 gramme. The residue left after digestion was transferred to a graduated cylinder and the final volume made up to 70 c.c. The proteolytic activity was indicated by the fact that digestion with 0.1 gramme papain left a residue of 18 c.c., while a blank measured 43 c.c. Other experiments described by Rippetoe show the inhibiting action of hydrochloric acid when present in quantities of 0.2 per cent. or 0.3 per cent.

H. M. Adams<sup>5</sup> again calls attention to the presence of starch, and points out the fact that pepsin may be detected by making a quantitative digestion of beef in the presence of 0.2 per cent. hydrochloric acid. Adam's method of assay is identical with that described by Graber, except that the medium employed is neutral instead of acid. Results are given showing the inhibiting action of 0.3 per cent. hydrochloric acid.

In a recent paper F. F. Shelley<sup>6</sup> has applied a modification of Sørensen's method, and offers a standard for pawpaw juice on the

<sup>4</sup> *Jour. Ind. and Eng. Chem.*, 4, 517 (1912).

<sup>5</sup> *Jour. Ind. and Eng. Chem.*, 6, 669 (1914).

<sup>6</sup> *Analyst*, 39, 170.

basis of the quantitative formation of carboxyl groups when casein is digested in slightly alkaline solution. R. Delaunay and O. Bailly<sup>7</sup> state that papain is a peptone-forming enzyme. They find that there is no relation between the proteolytic and milk-coagulation powers of papain. They recommend that the method of assay be based on the amount of protein dissolved in unit time.

The work which has been done in this laboratory for the purpose of standardization is based upon the work of Mendel and Blood,<sup>8</sup> and a number of commercial samples have been examined with the methods there given. We will therefore outline the methods used, tabulate our results, and, lastly, state our conclusions at the end of the paper.

### EXPERIMENTAL.

The methods other than those used in studying the proteolytic activity were those of the Official Agricultural Chemists.<sup>9</sup> The directions for the protein digestions were as follows:

*Preparation of Solutions.*—(a) Egg-white solution. Separate the whites of six freshly-laid eggs and, after beating slightly, dilute with two volumes of 1 per cent. sodium chloride solution. Mix. Filter through plaited filter paper. Make up to a definite volume<sup>10</sup> and mix thoroughly.

(b) Weigh one gramme of the papain and transfer to a dry 100 c.c. graduated flask. Do not make up the solution until everything is ready for the determination. The papain is then taken up with 1 per cent. salt solution, shaken thoroughly, and made exactly to volume. Exactly 30 minutes should elapse from the time the salt solution is poured upon the papain until the aliquots of the solution are taken.

(c) N/2 acetic acid.

*Determination of Proteolytic Activity at 80° to 100° C.*—Into a clean, dry 50 c.c. Erlenmeyer flask place 15 c.c. of standardized egg-white solution, add 1 c.c. of the papain solution and then 9 c.c. of 1 per cent. salt solution. All the digestions are made in a volume of 25 c.c. Transfer at once to the thermostat, already regulated at

<sup>7</sup> *Bull. Sci. Pharmacology*, 20, 141-7 (1913).

<sup>8</sup> *Jour. Biol. Chem.*, viii, 177 (1910).

<sup>9</sup> *U. S. Dept. Agr. Bur. of Chem. Bull.* 107 (revised).

<sup>10</sup> This solution should be so made that 15 c.c. contains 0.4000 gramme coagulable protein. This requires a preliminary determination and subsequent dilution.

80° C., and allow the digestion to proceed for exactly 15 minutes. Now add 1 c.c. of N/2 acetic acid and transfer immediately to a bath at 100° C. and heat for ten minutes. The time factor should be given the sharpest attention.

Bath at 80° C.—15 minutes.

Transfer—1 minute.

Bath at 100° C.—10 minutes.

In order to facilitate the acidification, a two-holed stopper is used, bearing a long glass tube to serve as a condenser, and a small funnel into which 1 c.c. of acetic acid can be easily placed.

The undigested protein is filtered off on a tared filter paper. Wash free from chlorides. Wash with 10 c.c. of 95 per cent. alcohol, and when this has passed through add 10 c.c. of ether U. S. P. Dry at 100° to 105° to constant weight.

At the same time that the above digestion is carried out, the amount of protein in the egg-white solution coagulable by heat is determined in a blank, *i.e.*, 15 c.c. of the same egg-white solution is mixed with 10 c.c. salt solution (or, better, 9 c.c. salt solution and 1 c.c. of the papain solution in which the enzyme has been destroyed by boiling vigorously for 15 minutes) and the operations are carried out upon this mixture exactly as described above.

Calculate the percentage of protein rendered non-coagulable under these conditions.

*Test for Pepsin in Papain.*—Take 15 c.c. of the same egg-white solution as prepared for the first digestion. Add 2 c.c. 1 per cent. salt solution, 3 c.c.<sup>11</sup> of N/2 HCl and, lastly, 5 c.c. of a 1 per cent. papain solution. Add 0.5 c.c. toluol to prevent putrefaction. Digest at 40° C. for 15 hours. Add 25 c.c. of a 10 per cent. solution of trichloroacetic acid. Heat to boiling on an electric stove. Boil ten minutes and filter through a tared paper, and wash the coagulum free from acid. Wash with alcohol and ether. Dry at 100° to 105° C. to constant weight. At the same time that this digestion is carried out the total amount of coagulable protein present should be determined in a blank experiment.

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<sup>11</sup> For the determination of the proteolytic activity at a concentration of 0.5 per cent. Na<sub>2</sub>CO<sub>3</sub>, 3 c.c. of a sodium carbonate solution (containing 0.125 gramme Na<sub>2</sub>CO<sub>3</sub>) was used instead of the N/2 hydrochloric acid. For the determination of the proteolytic activity at the alkalinity of the egg 3 c.c. of salt solution was used.

Calculate the percentage of protein digested under these conditions.

*Tryptophane Test No. 1.*—5 c.c. of 5 per cent. Witte's peptone in 1 per cent. salt solution, 5 c.c. of 1 per cent. papain extract in 1 per cent. salt solution (toluene, 1 drop). Add 1.2 c.c. 1.71 per cent. HCN solution, and 1.2 c.c. N/10 hydrochloric acid; total volume, 12.4 c.c. Digest in glass-stoppered bottles for 17 hours at 36° to 40° C. Add bromine water drop by drop.

*Tryptophane Test No. 2.*—5 c.c. of 5 per cent. Witte's peptone digested with 5 c.c. 1 per cent. papain solution and 1 c.c. HCN (1.71 per cent.) at 80° C. for 15 minutes should give a strong tryptophane test with bromine water. Report the intensity of the color in the following comparative terms: Faint, distinct, marked, strong, deep.

*Examination of Fictitious Sample.*—An apparently fraudulent sample gave the following analytical results: Digestion at 80° C., none; at 36° to 40° C. in 0.2 per cent. hydrochloric acid, 61.0 per cent. and 63.0 per cent.; at 36° to 40° C., at the alkalinity of egg,

TABLE I.

#### *Examination of Samples of Dried Pawpaw Latex Containing no Diluents.*

[illegible]

TABLE II.  
*Examination of Papain Samples Containing Starch as a Diluent.*

Laboratory No. ....	3042	3077	3034	3043	962	2993	2921	3084	3041	3076	3167	3036	3038	3046
Digestion at 80° C., blank.....	0.383	0.406	0.409	0.400	0.406	0.410	0.400	0.413	0.410	0.403	0.383	0.399	0.403	0.403
Residue.....	0.200	0.200	0.213	0.253	0.236	0.203	0.237	0.369	0.387	0.311	0.297	0.321	0.376	0.311
Per cent. digested.....	48.3	50.7	47.9	36.7	41.4	50.5	40.8	10.7	5.6	20.3	22.4	19.5	6.7	22.8
Digestion at 40° (a) 0.2 per cent. HCl, blank.....	0.441	0.433	0.424	0.440	0.440	0.401	0.427	0.435	0.424	0.409	0.441	0.396	0.429	0.428
Residue.....	0.444	0.447	0.436	0.439	0.427	0.406	0.418	0.428	0.412	0.403	0.441	0.393	0.414	0.431
Per cent. digested.....	None	None	None	None	2.9	None	1.8	1.6	None	1.5	None	None	3.5	None
(b) Alkalinity of egg, blank.....	0.430	0.422	0.424	0.425	0.427	0.406	0.430	0.434	0.417	0.408	0.435	0.396	0.429	0.428
Residue.....	0.440	0.407	0.408	0.425	0.414	0.407	0.415	0.422	0.415	0.405	0.434	0.384	0.414	0.418
Per cent. digested.....	None	3.5	3.8	None	3.0	None	3.5	2.7	None	None	None	3.3	3.5	2.3
(c) 0.5 per cent. Na <sub>2</sub> CO <sub>3</sub> , blank.....	0.430	0.422	0.424	0.425	0.427	0.431	0.430	0.429	0.424	0.408	0.435	0.396	0.425	0.428
Residue.....	0.430	0.421	0.438	0.439	0.429	0.419	0.433	0.431	0.412	0.412	0.441	0.403	0.416	0.438
Per cent. digested.....	None	None	None	None	None	2.7	None	None	2.8	None	None	None	2.1	None
Tryptophane test, 40°.....	Deep	Marked	Distinct	Marked	Strong	Strong	Strong	Faint	Trace	Faint	Faint	Faint	None	Strong
Tryptophane test, 80°.....	Deep	Marked	Marked	Strong	Faint	Trace	Strong	Faint	Trace	Faint	Faint	Faint	None	Distinct
Nitrogen.....	7.81	7.52	7.61	6.20	5.87	7.27	5.44	2.77	2.43	3.97	3.73	2.83	2.14	3.08
Starch.....	15.12	15.1	20.11	22.9	20.48	23.71	32.13	43.88	46.22	46.46	52.65	53.51	55.31	57.78
Moisture.....	8.38	8.35	8.27	8.63	11.89	8.8	6.07	9.0	9.39	9.25	10.85	9.20	10.94	7.92
Ash.....	8.62	8.51	7.87	7.50	6.40	7.29	7.06	1.90	2.30	3.49	2.98	3.76	1.40	3.25
Sugar reducing <sup>1</sup> .....	None	None	None	0.47	None	None	None	7.32	None	None	None	None	3.26	0.75
Sugar non-reducing <sup>2</sup> .....	None	None	Trace	None	None	None	None	11.19	None	None	None	None	None	None
Digestion at 80° C. without added starch (calculated).....	56.9	59.7	59.9	47.6	52.1	66.2	60.1	28.5	10.4	37.9	47.3	41.9	15.0	54.0
Nitrogen (calculated).....	9.2	8.9	9.3	8.05	7.3	9.5	8.0	4.9	4.5	7.4	7.8	6.08	4.7	7.3
Ash (calculated).....	10.1	10.0	9.8	9.7	8.0	9.5	10.4	3.4	4.2	6.5	6.3	8.0	3.1	7.7

<sup>1</sup> As dextrose.<sup>2</sup> As sucrose.



there was no digestion, and the same result was obtained when the digestion was carried out in a medium of 0.5 per cent.  $\text{Na}_2\text{CO}_3$ . It gave negative tryptophane tests under both conditions. Nitrogen,

TABLE III.  
*Examination of Papain Samples Containing Sugar as Diluent.*

Laboratory No. ....	3118	3037	3083
Digestion at 80° C., blank. ....	0.400	0.399	0.421
Residue. ....	0.274	0.298	0.327
Per cent. digested. ....	31.5	25.3	22.3
Digestion at 36° to 40° C.:			
(a) 0.2 per cent. HCl, blank. ....	0.422	0.408	0.406
Residue. ....	0.214	0.215	0.216
Per cent. digested. ....	49.3	47.2	47.0
(b) Alkalinity of egg, blank. ....	0.428	0.407	0.438
Residue. ....	0.422	0.401	0.435
Per cent. digested. ....	1.4	1.5	None
(c) 0.2 per cent. $\text{Na}_2\text{CO}_3$ , blank	0.428	0.408	0.439
Residue. ....	0.423	0.410	0.440
Per cent. digested. ....	1.0	None	None
Tryptophane test, 40° C. ....	Distinct	Marked	Distinct
Tryptophane test, 80° C. ....	Faint	Faint	Faint
Nitrogen. ....	5.79	6.15	5.81
Starch. ....	None	None	None
Moisture. ....	4.14	....	....
Ash. ....	9.95	4.11	4.21
Sugar, reducing <sup>1</sup> . ....	24.75	24.5	25.65

<sup>1</sup> Calculated as lactose.

1.3 per cent. and 1.34 per cent.; starch, none; moisture, 9.59 per cent.; ash, 4.05 per cent. Reducing sugar was determined after inversion with hydrochloric acid, and when calculated as glucose amounted to 73.75 per cent.

#### SUMMARY.

1. In these digestions with pawpaw juice it has again been shown that the digestion proceeds rapidly at 80° to 100° C. This characteristic property can be utilized for the standardization of commercial papain samples.

2. Under the conditions outlined above, dried pawpaw juice should be capable of dissolving at 80° to 100° C. not less than 40 per cent. of the egg-albumin taken.

3. No samples of "papain" were found upon the market which had a higher digestive activity than the samples of dried pawpaw latex under the conditions employed.

4. Since the use of the term "papain" has given rise to the conditions pointed out in this paper, we are inclined to the view that papain products ought to be marketed as "dried pawpaw juice," and that only a lower limit of digestive strength should be stated in defining a standard for it. A definition proposed upon this basis might be stated as follows: Dried pawpaw juice is the dried albuminous exudate of the fruit of *Carica Papaya*. L. (Fam. Papayacæ), free from starch, sugars, and diluents, and contains a proteolytic enzyme or enzymes. When assayed by the method above<sup>12</sup> it has the power of digesting at 80° to 100° C. not less than 40 per cent. of the unaltered egg-white protein.

5. Of twenty-six samples studied, seven represented the undiluted dried latex, fifteen contained starch in amounts varying from 15 per cent. to 58 per cent., while three were diluted with sugar and one with dextrin. Four samples showed a high digestive strength under conditions favorable for pepsin digestion. On the basis of the standard proposed above, twelve samples, or 44 per cent., have been diluted to such an extent that their digestive strength is below a very reasonable requirement.

CHEMICAL RESEARCH LABORATORY OF THE UPJOHN COMPANY,  
Kalamazoo, Mich.

## PURE DRUGS AND THE PUBLIC HEALTH.\*

By MARTIN I. WILBERT.

Assistant in Pharmacology, Hygienic Laboratory, United States Public Health Service.

Food and drug laws are generally recognized as being economic measures designed to prevent dishonest practices or gross adulteration and thereby secure to the purchaser an equitable return and the assurance that the food or drug product purchased will be true to name or nature as represented by the seller. The pure drug features of these laws, however, combined with the laws designed to restrict the practice of pharmacy to specially trained and capable individuals, also have, or should have, an evident bearing on public health in that the purchaser is led to assume that the licensed druggist is directly responsible for the character and purity of the drugs sold.

<sup>12</sup> See page 545.

\* Reprinted from the Public Health Reports, vol. 29, No. 19, May 8, 1914.

The methods adopted for enforcing these laws in the past have not always been in accord with the securing of the best results from a public-health point of view, and even in States where the control of laws regulating the nature and purity of drug products is in the hands of the State board of health the tendency has been to discourage rather than encourage adequate and satisfactory control of all medical supplies.

Some indication of the nature and variability of the products sold as medicine may be had from a comparative study of Hygienic Laboratory bulletins embodying in the form of annual compilations a "Digest of Comments on the Pharmacopœia of the United States and on the National Formulary."

These bulletins, though not compiled especially for this purpose, reflect from year to year the available material regarding published activities of food and drug laboratories so far as they relate to pharmacopœial or official drugs and preparations, and the sum total of the reported activities well indicates the general trend of the trade so far as it is influenced by the present-day method of drug-law enforcement.

A compilation of the analytical reports embodied in previously published bulletins shows that out of a total of more than 9000 samples of 6 pharmacopœial preparations reported on during the years 1907 to 1911, inclusive, more than 4000, or approximately 45 per cent., were found to be not in compliance with the requirements of the Pharmacopœia. That approximately this same ratio still holds is evidenced by the available annual reports of State boards of health and State food and drug commissioners, abstracted in Hygienic Laboratory Bulletin No. 93, embodying a Digest of Comments on the Pharmacopœia of the United States and on the National Formulary for the calendar year ending December 31, 1912. Among the reports reflected in this bulletin we find that the chemist of the Indiana board of health states that of 365 samples of drugs analyzed 156, or 42.7 per cent., were illegal in that they did not comply with the standards or requirements. The food and drug commissioner of South Dakota reports that of 326 samples examined 118, or 36.3 per cent., were not passed, and in New Hampshire of 421 samples of drugs examined by the chemist of the board of health 180, or 42.8 per cent., were not conformable.

Further evidence regarding existing conditions will be found in the accompanying table showing the total number of samples of

26 drugs and preparations reported on during 1912, the number that were rejected or found to be illegal, and the number of reporters on each individual article.

TABLE SHOWING REPORTED RESULTS OF ANALYSIS OF SAMPLES OF 26 OFFICIAL ARTICLES—A COMPILATION OF DATA INCLUDED IN HYGIENIC LABORATORY BULLETIN No. 93.

	Number of reporters	Number of samples		Per cent. of samples rejected
		Examined	Rejected	
Alcohol.....	7	98	47	47.9
Ammonia, aromatic spirit of....	5	116	78	67.2
Ammonia, water.....	4	19	11	57.8
Asafoetida.....	10	256	200	78.1
Belladonna, tincture of.....	3	14	6	42.8
Camphor, spirit of.....	19	802	423	52.7
Camphor, liniment of.....	8	597	99	16.5
Ferric chloride, tincture of.....	7	680	219	32.2
Ferrous iodide, sirup of.....	8	549	88	16.0
Ginger, tincture of.....	9	74	30	40.5
Iodine, tincture of.....	18	984	474	48.1
Lard.....	8	265	53	20.0
Lemon extract.....	10	252	100	39.6
Lime water.....	10	635	98	15.4
Linseed oil.....	12	367	138	37.6
Olive oil.....	13	912	69	7.5
Opium, camphorated tincture of.	5	91	30	32.9
Opium, tincture of.....	11	252	125	49.6
Peppermint, spirit of.....	14	270	139	51.4
Solution of hydrogen dioxide....	13	1,026	90	8.7
Solution of potassium arsenite...	7	570	128	22.4
Sulphur.....	6	70	35	50.0
Sweet spirit of nitre.....	22	609	336	55.1
Turpentine, oil of.....	8	639	132	20.6
Vanilla.....	12	286	116	40.5
Witch hazel.....	5	91	24	26.3
Total.....		10,524	3,288	31.2

As an object lesson this table is well worth studying from various points of view. Not the least important in this connection is the suggestion that, despite the apparently large number of samples examined, the present-day method of enforcing food and drugs laws is hopelessly inadequate so far as offering to control, even in a moderate degree, the nature and purity of drug products as they reach the consumer.

The limitations imposed by the present method of enforcing the drug feature of food and drugs laws is well illustrated by a table recently published by L. P. Brown, food and drug commissioner of

Tennessee (*Am. Food J.*, 1912, v. 7, July, p. 9), showing the number of States in which food and drugs laws are actually being enforced, the number of employees in each State, and the number of samples analyzed in one year. This table states that no less than 44 political divisions of the United States makes some attempt to enforce laws of this type. The total number of employees recorded is 465, an average of but 10 to each State. The total number of samples examined during one year is given as 83,498, and from a study of several annual reports it is fair to assume that not more than from 20 to 25 per cent. of these samples represent drug products or products used as drugs.

When one remembers that in the United States alone there are no less than 40,000 retail drug stores, and that each one of these stores has in stock from 1000 to 20,000 separate articles used or offered for use as medicine, the futility of endeavoring to control or even to seriously influence the nature and purity of products sold as medicines by an occasional examination of one or more preparations is at once apparent.

That the present-day method of enforcing food and drugs laws is efficient in some directions must be admitted, and the possibilities in this line are well indicated in the above table. Given a product that is more or less easily examined by chemical means and for which a reasonably high standard has been established by the Pharmacopœia, by statute, or by regulation, little or no difficulty is encountered in materially improving the conditions under which such an article is marketed, and thus securing for the consumer a reasonably reliable product if he will but exercise ordinary care in making his purchases from reputable dealers.

One instance of this type is olive oil, which up to a comparatively few years ago was considered to be among the most adulterated of all commercial products. This oil, though largely, if not preponderatingly, used as a food product, is also of value as a medicine and can now be classed among the generally pure articles used for medicinal purposes.

Another article that has been materially improved through systematic examination and accompanying publicity is "solution of hydrogen peroxide." This preparation is also used quite extensively in the arts as a bleaching material, and formerly it was quite common to find the comparatively impure and usually weak technical product on sale in drug stores for medicinal purposes. Improved methods of manufacture, the use of preservatives, and the exercise

of a little additional care in keeping the preparation have evidently combined to change this preparation from one that was considered to be uniformly impure to one that complies fairly well with the spirit though not the exact letter of the present pharmacopœial requirements. Disregarding the frequent presence of a preservative, only 8.7 per cent. of the preparations examined were found to be deficient in strength or contaminated. This figure, when one considers the unstable nature of the product, compares very favorably, indeed, with the low percentage (7.5 per cent. of samples of olive oil rejected during the same period).

Oil of turpentine is another product that is rapidly being improved, and the economically closely related linseed oil, while still above the general average for all of the products reported on during 1912, also evidences a marked improvement over previously reported conditions. These two products are very widely used for technical purposes and occupy rather an anomalous position as drugs. The frequency with which they are now found to be of inferior quality is no doubt due to the fact that little or no attempt has as yet been made to regulate their identity or purity for technical purposes, and because of the much lower price of the impure technical products they are very frequently sold in place of the official, or pharmacopœial, articles for medicinal use.

The opposite of these rather promising conditions is shown in connection with asafœtida, a drug product of somewhat uncertain value that is, nevertheless, used quite extensively, largely perhaps because of its penetrating odor and disagreeable taste. The pharmacopœial requirements for this drug are unnecessarily high and the chemical tests for identity and purity quite inadequate. It is, therefore, not at all surprising to learn that more than 78 per cent. of the samples of asafœtida examined did not comply with the requirements of the Pharmacopœia.

This drug is, however, but one of a number of articles that are of uncertain medicinal value, are difficult to control from a chemical point of view, and are more frequently found to be below standard than above. This one fact, that there are hundreds of more or less widely used drugs for which we have little or no data on which to base a chemical control of the finished preparation, serves to further illustrate the difficulty of exercising any adequate control of medicinal preparations through a city, State, or Federal laboratory.

That some form of control is essential is evidenced by the head

of one of the leading drug houses in England, who is reported as saying that the thousands of samples of crude drugs examined annually in his laboratories yield abundant evidence to show that constant and efficient control is necessary if the purity of medicinal products is to be maintained and progress achieved on the lines of modern science.

The reports of the several officials intrusted with the enforcement of laws relating to the production and sale of drugs have emphasized time and again that much of the material that is now being sold as medicine in this country is either directly harmful or absolutely useless, and that from a public-health point of view considerable progress is necessary before the consumer is as adequately safeguarded as he should be.

It is generally recognized that once a seal is broken, a package opened, or a cork drawn, the manufacturer can no longer be held responsible for the content of the package, and, quite irrespective of the nature of the medicine, the pharmacist in dispensing a portion of an original package assumes all responsibility for the nature and purity of the article.

That this responsibility of the pharmacist is as yet not appreciated and that much progress must be made in the enforcement of existing laws before the public is as adequately protected as it should be, or has a right to expect, is evidenced by the shortcomings of the pharmaceutical preparations included in the table referred to above, particularly those preparations usually made on a comparatively small scale in the retail drug store. From the point of view of State or national officials, these preparations offer the most serious difficulties in the way of control, through the intervention of Federal or State laboratories, and yet they are of considerable importance from a medical point of view in that they include some of the most widely used medicines we now have. It has been well said that medicine, particularly the use of medicines, as a science can make little or no progress until physicians know more of the nature and composition of the articles they use as medicines and of the action or influence of these articles on the healthy as well as the diseased organisms.

How little actual reliance can be put in the average drug preparation at the present time will be appreciated when we learn that fully 50 per cent. of such widely used articles as aromatic spirit of ammonia, spirit of camphor, tincture of iodine, tincture of opium, spirit

of peppermint, and spirit of nitrous ether have been found to be adulterated or below standard.

Some additional argument for more adequate control of the identity, purity, and strength of materials used as medicine is offered by the table including a compilation of data showing the variability of well-known and widely used drugs which can, in a measure at least, be controlled by assay and analysis. Preparations of these drugs, on assay, are less frequently found to be above than below standard, and even a standardized preparation is far from being permanently so.

TABLE SHOWING VARIATIONS IN THE ACTIVE PRINCIPLES OF DRUGS REPORTED DURING THE CALENDAR YEAR ENDING DECEMBER 31, 1912.

[A compilation of data included in *Hygienic Laboratory Bulletin No. 93*.]

	Num- ber of re- porters	Num- ber of sam- ples.	Mini- mum per cent.	Maxi- mum per cent.	U. S. P. requirements.
Belladonna leaves..	5	144	0.175	0.563	0.3 per cent. mydriatic alkaloids.
Belladonna root...	6	115	.11	.780	0.45 per cent. mydriatic alkaloids.
Guarana.....	3	41	3.720	5.16	3.5 per cent. alkaloidal principles.
Hydrastis.....	8	114	2.3	4.85	2.5 per cent. hydrastine.
Hioscyamus.....	4	120	.043	.234	0.08 per cent. mydriatic alkaloids.
Ipecac.....	10	253	1.24	2.75	1.75 per cent. ipecac alkaloids.
Jalap.....	6	173	3.67	21.76	7 per cent. total resin.
Stramonium.....	4	127	.14	.470	0.25 per cent. mydriatic alkaloids.

As is well known, all pharmaceutical preparations and many drugs and chemicals deteriorate on keeping, and this deterioration is not so much dependent on time alone as a number of accompanying factors, as light, heat, atmospheric conditions, and the general lack of care or technical knowledge in storing the various substances. All in all, it is safe to assert that no matter how excellent a drug or preparation may be when it leaves the producer there are many possibilities for it to become worthless, if not positively dangerous, through carelessness or neglect before it reaches the consumer.

The general subject of changes produced in a drug because of deterioration due to improper keeping has received altogether too little attention and it is not generally recognized that many of the formerly well known drugs have probably been discredited because of their failure to accomplish the object for which they were administered, a failure perhaps largely due to some form of contamination or to decomposition not recognized by the dispenser.

In addition to the changes in drugs that may be produced by heat,



by the constituents of the air, by ferments, or by microörganisms, some recent observations by Neuberg, of Berlin, suggest that nearly all types of organic compounds acquire a pronounced photosensitive-ness when they are mixed with inorganic compounds. Iron salts, it is said, provoke such changes most strikingly, and it is quite possible that otherwise innocuous materials may thus be converted, in part at least, into decidedly harmful compounds.

In addition to this possible deterioration of medicaments, which can be averted, to a considerable degree at least, by constant care and watchfulness, there are a number of other factors that should be taken into consideration in connection with the dispensing of medicines to the consumer. Not the least important of these several factors is the accuracy and also the sensitiveness of scales, weights and measures. On page 43 of Hygienic Laboratory Bulletin No. 93 will be found several references that bear out this assertion. One observer found that not one of 36 graduates examined was correct. Some were better than others, but all were bad. In the State of Kansas nearly one-half of the prescription weights examined were condemned, and of the 718 prescription scales examined 195 were found to be unfit for use.

The inability or unwillingness of retail druggists to assume proper responsibility is further evidenced by the recommendation of one man to use ready-made tablets in place of weighing out small quantities of potent drugs. The fallacy of this advice has more latterly been emphasized by the fact that compressed as well as other tablets, even under most favorable conditions, may vary from 10 to 30 per cent. from the quantities claimed. Under conditions not so favorable even greater variations have been observed, and in cases where tablets have been made to sell at inordinately low prices it has been found that expensive chemicals were present only in traces sufficient to give qualitative tests.

In conclusion it may be reiterated that the more evident shortcoming in the present-day enforcement of pure-drugs laws is the general failure to properly place the responsibility for the nature, kind, and purity of the medicines supplied to the consumer where it belongs. This shortcoming is being corrected, to some extent at least, by recently enacted laws to regulate the practice of pharmacy by placing the responsibility squarely on the person dispensing the drug.

The proper enforcement of laws designed to regulate the practice

of pharmacy in conjunction with pure-drugs laws should relieve physicians and the public of any doubt as to the composition, purity, quality, and strength of all drugs and medicinal preparations used in the treatment of disease. As these laws are enforced at the present time it is plainly evident that the methods of control are inadequate and do not serve to safeguard public health as well as they could or should.

Boards of health and other State and Federal officials intrusted with the enforcement of these laws should endeavor to call attention to the desirability of having druggists exercise a close scrutiny of the drugs and preparations included in their stock, to keep drugs, chemicals, and preparations in suitable containers, to throw away old or useless material, and to see that scales, weights, and measures are reliable and accurate under the conditions imposed upon them.

Some effort should also be made to see that drug stores are equipped with the necessary analytical apparatus with which to analyze or examine all supplies and thus assist in maintaining a more efficient control of the articles sold as medicine.

Consistent and efficient control of the identity, purity, and strength of all drugs and preparations as furnished the consumer would make for progress in the science of medicine and should prove to be an important factor in promoting public health.

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## PROGRESS IN PHARMACY.

### A QUARTERLY REVIEW OF SOME OF THE MORE INTERESTING LITERATURE RELATING TO PHARMACY AND MATERIA MEDICA.

By M. I. WILBERT, Washington, D. C.

The changes in values of medicinal products of all kinds continue to attract general attention in the drug trade. Stocks of a number of chemicals, as well as many of the foreign botanical drugs, have been practically exhausted, and the prices asked for these substances remain high. In connection with many other drugs, prices have decreased to some extent, and market conditions generally are now fairly well fixed. The values of opium and its alkaloids remain high, as do prices for nearly all drugs and chemicals of German or of Austrian origin. Prices for mercurials of all kinds, Russian paraffin oil, thymol, phenol and phenol products generally

are unusually high, and, because of the scarcity of these products, still have an upward tendency.

In Great Britain the war is bringing about a peculiar condition of affairs which may ultimately have a far-reaching, disturbing influence on patent law enforcement. A recent report (*Pharm. J.*, 1914, vol. 93, p. 569) states that the Board of Trade has granted the application of Mr. S. Wellcome for a license to manufacture and sell in Great Britain the drug salvarsan, or "606." The registration of the trade-mark has been suspended for the time being, and it is proposed that patents for other chemicals of German origin not now worked in Great Britain will also be suspended.

*The New British Pharmacopœia* was placed on exhibition for review in London on October 1, and will be available to the book trade on December 31, 1914. In general appearance the new Pharmacopœia closely resembles the British Pharmacopœia now official, the size of the two books being approximately the same, despite the 67 additional pages in the new pharmacopœia, the discrepancy being accounted for by the use of somewhat thinner paper. The general impression imparted by the printed page is that the type and arrangement of the material is practically the same.

The several British pharmaceutical journals have presented elaborate reviews of the Pharmacopœia, and one wholesale house, Messrs. Southall Bros. & Barclay, Ltd., of Birmingham, has distributed a pamphlet, of 24 pages of comments on the new Pharmacopœia, so that the available literature on the book is already quite extensive.

From the reviews which have appeared in the several journals it would appear that the deletions from the British Pharmacopœia are chiefly of drugs and preparations, while the additions are mostly long overdue and include 25 chemicals, 24 galenical preparations, and 3 crude drugs.

The alterations in strength are of considerable moment and are being actively discussed in British pharmaceutical journals. The provisions of the Brussels Conference Protocol have generally been followed, special attention being directed to the exceptions made. The proposed international drop counter is recognized, the dropping device being described.

Metric weights and measures only are to be used in making or testing official products; the term "mil" is recognized as a short

official designation to be used in place of the more cumbersome cubic centimetre. Imperial weights and measure appear only in connection with the doses.

The Latin nomenclature employed in the Ph. Brit. V. has much in common with that employed in our own Pharmacopœia of the United States, and a table of abbreviations of Latin names of official drugs and preparations appears in the index. This has been somewhat roughly handled by the British reviewers.

An editorial (*Chem. and Drug.*, 1914, vol. 85, p. 480) says: "It is hoped that the abbreviations included in the Ph. Brit. V. will never be put forward as legally binding. They do not appear to be at present, but the list should not go unnoticed; many of the abbreviations are horrible."

Considerable attention has been devoted to the lead and arsenic limits in a number of chemical substances. Tables reproduced in the British pharmaceutical journals show that limits have been fixed for a total of nearly one hundred official substances.

The number of crude drugs and their preparations which are required to be standardized has been increased, and the methods of assay have been brought up to date.

From the available comments it would appear that the pharmacists of Great Britain are still somewhat dissatisfied with the method of revising the Pharmacopœia, but that the book, despite its many shortcomings, is nevertheless a great improvement over its immediate predecessor.

The publication of the British Pharmacopœia has again revived interest in Great Britain in the subject of local pharmacopœias. In a recent discussion of the subject (*Pharm. J.*, 1914, vol. 93, p. 550) it is pointed out that booklets of this nature are intended for permanent use and that there is no reason why they should not be fashioned after a good model so as to make them not alone useful but also attractive to medical practitioners for whom they are intended.

In our country the failure to enact the *Harrison bill* into law before the adjournment of the second session of the sixty-third Congress was rather widely deplored. Despite the opposition that has been manifested at times, it is generally recognized that the Harrison bill is in no way a regulatory measure, but that it is likely to be of considerable value in this respect because of its being designed to fur-

nish the information necessary to make State and other local regulatory measures operative. The text of the bill as finally agreed upon in the Conference Committee is acceptable to physicians and pharmacists generally, though many believe that it is unnecessarily comprehensive and will entail a greater expenditure of time and money to enforce than is necessary to attain the objects aimed at. In the event that the Conference Report is agreed to by the Senate and the bill is signed by the President, the new law will become operative on March 1, 1915.

*Proprietary Remedies.*—The report of the Select Committee of the House of Commons on Patent Medicines has been published as a separate volume of 782 pages, and is now available through the book trade at 6s. 7d., or, with the somewhat elaborate index, 7s. 6d. The book contains, in addition to the findings of the committee, a verbatim report of the evidence of 42 witnesses who appeared before the committee at the 33 public sittings held from May 12, 1913, to June 12, 1914. One of the abuses commented on by the Select Committee is the fact that the government, in a way, is a party to fraudulent practices because of the collecting of a stamp duty on "patent" medicines or secret nostrums, which stamp carries with it at least the suggestion of recognition or endorsement by the government.

In this connection pharmacists in this country are to be commended for their activity in opposing the imposition of a stamp tax on patent medicines. Many medical practitioners and pharmacists feel that such a tax would, in a way, be an endorsement of these products and would give them a standing not at all in keeping with our present-day knowledge regarding the possibilities and limitations of drugs and medicines.

Roemer, John, in a general discussion of the patent-medicine problem, expresses the opinion that pernicious nostrums can be consistently divided into six classes:

1. Those that bear false statements.
2. Those whose claims for medicinal virtue are exaggerated.
3. Those that contain narcotics.
4. Those that contain alcohol in disguise as medicine.
5. Those that are exploited for venereal diseases.
6. Those that are exploited by subterfuge as emmenagogues.

Such preparations as may be included in the above classification

can claim no justifiable right of existence, much less sanction or tolerance for sale through legitimate pharmacy.—*Proc. New York Pharm. Assoc.*, 1914, p. 286.

The rapid growth of pharmaceutical manufacture in this country is commented on in an article entitled "Drug Intoxication," published in *Public Health Reports* (October 16, 1914, vol. 29, p. 2767), and the suggestion is made that the steady increase in the death-rate from so-called degenerative diseases may be in a measure accounted for by the injuries brought about by the promiscuous use or abuse of actively poisonous drugs.

*Bromide Rash*.—Weiss, Ludwig, reports an unusual case of bromoderma of the leg in a female, aged 24, who had taken potassium bromide for a number of years.—*J. Am. M. Assoc.*, 1914, vol. 63, pp. 635-639.

*Suicides and Newspaper Publicity*. (Anon.)—The probable influence of newspaper publicity of details with regard to the nature and kind of substances used in connection with cases of poisoning is well shown by a compilation from the reports of the coroner of St. Louis for the years 1910 to 1914, inclusive. The figures given suggest the desirability of telling the truth in regard to the action of corrosive poisons and the need for refraining from even an intimation that the use of any one poison or substance may lead to a sure and painless death.—*J. Am. M. Assoc.*, 1914, vol. 63, pp. 600, 601.

*Poisons and Habit-forming Drugs*.—Progress in the way of legislation to restrict the sale and use of poisons and habit-forming drugs is reviewed in the introduction to a second supplement to *Public Health Bulletin No. 56*. This supplement, the introduction to which appears in *Public Health Reports* for November 13, 1914, includes a digest of laws and regulations relating to the possession, use, sale, and manufacture of poisons and habit-forming drugs enacted during 1913 and 1914. The compilation should be of considerable interest to pharmacists in all parts of the United States who may be called upon to endorse or to oppose prospective legislation along this line.

*Solid Alcohol*.—The use of solidified alcohol for rubbing and for general disinfection purposes is meeting with increasing popularity. The production of alcohol in solid form would appear to offer a

possibility for denaturing the product in such a way as to make the tax-free article available for external use in medicine.

*Amylum.* (Southworth, Thomas S.)—While it is an established fact that even young infants are prepared to digest moderate quantities of boiled starch, the indication for its use appears to lie in those suffering from disturbances of digestion and nutrition. The chief end subserved by the addition of starch is not solely to nourish the infant, but to promote nutrition by making possible a more orderly digestion and absorption of its main nutriment, milk.—*J. Am. M. Assoc.*, 1914, vol. 63, p. 1377.

*Camphor.* (Cairis, Valentine.)—The comparative toxicity of camphor in different vehicles. In the undissolved state the lethal dose of camphor in the digestive system of the guinea-pig is between 0.14 and 0.18 Gm. per 100 Gm. body weight. In ether-alcohol solution the toxicity is markedly increased. Dissolved in oil, it is notably less poisonous. When given hypodermically, the toxicity of camphor in oily solutions is far below that in alcohol and water, and in all cases is greater than the effect produced by oral administration. The toxicity is much higher by peritoneal injection than by any other way of administration; but by this method the oily solution is still the least toxic of any.—*J. Pharm. Chem.*, 1914, vol. 10, p. 224; *Pharm. J.*, 1914, vol. 93, p. 457.

*Cottonroot Bark.*—Power and Browning report a chemical examination of cottonroot bark. No alkaloid is contained in the bark, and no evidence could be obtained of the presence of tannin.—*Pharm. J.*, 1914, vol. 93, p. 423.

*Ergot.* (Rosenbloom and Schildecker.)—The successful isolation of ergotin in crystals from certain organs in a case of acute ergot poisoning.—*J. Am. M. Assoc.*, 1914, vol. 63, pp. 1203, 1204.

*Ipecac.* (Hesse, O.)—Ipecamine and hydroipecamine, two new alkaloids, were found in the course of an investigation of the alkaloidal constituents of ipecacuanha.—*Liebig's Annalen*, 1914, vol. 403, p. 1; *Pharm. J.*, 1914, vol. 93, p. 425.

*Mercuric Benzoate.* (Rupp and Hermann.)—Mercuric benzoate, which is official in the French Pharmacopœia, has been recommended as the most suitable salt for hypodermic injection. Since it is a normal salt it is not apparent why it should be less ionized in solution than any other mercuric salt.—*Arch. d. Pharm.*, vol. 252, No. 3; *Pharm. J.*, 1914, vol. 93, p. 323.

*The Prognosis in Morphine Addiction.* (König, H.)—The prognosis naturally varies according as the addiction was acquired in connection with a chronic painful affection, such as tabes, neuralgia, or peritoneal adhesions, or with single periods of pain, such as gall-stone colic, or in connection with periods of melancholia or insomnia. Experience with 28 cases is reviewed, demonstrating a successful outcome in over 50 per cent. of the 14 in the gall-stone group. The treatment required from three to ten months in these cases.—*Berl. klin. Wchnschr.*, vol. 51, June 1, No. 22; *J. Am. M. Assoc.*, 1914, vol. 63, p. 204.

*Commercial Papain and Its Assay.* (Adams, H. M.)—Commercial papain is sometimes adulterated with starch or pepsin. The presence of starch is shown by the addition of iodine solution, and the pepsin by comparative observations on the digestion of meat in a weak acid and in a neutral or alkaline solution. To determine the proteolytic power of papain, neutral solutions give the most satisfactory results with either meat or the whites of eggs.—*J. Ind. and Eng. Chem.*, 1914, vol. 6, pp. 669, 670.

*Acitrin.*—Phenolcinchoninic acid ethylester, a yellowish, odorless, and tasteless powder, melting at 59°, only slightly soluble in organic solvents. On boiling with acids or alkalis the ester is saponified.—*Südd. Apoth.-Ztg.*, 1914, vol. 54, p. 137.

*Agar-agar Biscuits.* (Anon.)—To make agar-agar biscuits it is only necessary to add the fine agar-agar to the flour used in making the biscuits. The amount should be, if possible, sufficient so that a dose (5 grammes) may be included in each biscuit.—*J. Am. M. Assoc.*, 1914, vol. 63, p. 1224.

*Algocratine.*—Mannich and Leemhuis report an examination of a powder offered as an infallible remedy for migraine, neuralgia, grippe, influenza, and other diseases. The preparation was found to consist essentially of a mixture of phenacetin, 50 Gm., caffeine, 10 Gm., and pyramidon, 40 Gm. The claims made for the composition of the preparation were found to be quite untrue.—*Apoth.-Ztg.*, 1914, vol. 29, p. 553.

*Amphotropin.*—A combination of camphoric acid and hexamethylenetetramine,  $C_5H_{14}(COOH)_2[(CH_2)_6N_4]_2$ . A white crystalline powder having an acid reaction, soluble in 10 parts of water at room temperature, more readily soluble in hot water and in alcohol.—*Südd. Apoth.-Ztg.*, 1914, vol. 54, p. 137.



*Apendicol.* (Mannich and Leemhuis.)—This name is applied to a paraffin oil colored red and containing a minute quantity of fruit ether as a flavor.—*Apoth.-Ztg.*, 1914, vol. 29, p. 672.

*Apyron.* (Anon.)—Lithium acetylsalicylate. Contains 96.26 per cent. of acetyl salicylic acid and 3.74 per cent. of lithium.—*Chem. and Drug.*, 1914, vol. 85, p. 376.

*Arsylate.* (Anon.)—Dimethyl aminotetramido-arseno-benzene. A liquid easily absorbed in subcutaneous injection. It is a substitute for salvarsan.—*Chem. and Drug.*, 1914, vol. 85, p. 376.

*Atrinal.* (Anon.)—Atropine-sulphonic acid, a new mydriatic preparation manufactured by the Hoffmann-La Roche Company.—*Chem. and Drug.*, 1914, vol. 85, p. 376.

*Catin.* (Mannich and Leemhuis.)—A preparation marketed under this name was, on examination, found to consist of zinc sulphocarbonate.—*Apoth.-Ztg.*, 1914, vol. 29, p. 694.

*Cerephysin.*—The name applied to an extract made from the infundibular portion of the hypophyses of cattle. One cubic centimetre of cerephysin corresponds to 0.2 Gm. of moist organ substance. It occurs as a clear water-white liquid dispensed only in ampoules.—*Südd. Apoth.-Ztg.*, 1914, vol. 54, p. 137.

*Chineonal.* (Erdt, V.)—Fatal poisoning in a child of three who swallowed nine tablets of chineonal tablets during the day. The child had taken in the tablets the equivalent of 0.648 gramme of veronal in six or eight hours.—*Münch. med. Wchnschr.*, vol. 51, August 25, No. 34; *J. Am. M. Assoc.*, 1914, vol. 63, p. 1431.

*Collargol.* (Cromwell, Andrew J.)—Collargol in pyelography, with a report of an interesting case and a note on a number of experiments on dogs. From the pathologic findings and from the experimental work on dogs the author is convinced that the use of collargol in pyelography is not without danger, and that efforts should be made to secure a substance less harmful for this purpose.—*J. Am. M. Assoc.*, 1914, vol. 63, pp. 1387-1389.

*Digimorval.* (Anon.)—Each tablet is said to contain 0.005 Gm. of morphine and 0.05 Gm. of powdered digitalis and 3 drops of mentholvalerianate.—*Südd. Apoth.-Ztg.*, 1914, vol. 54, p. 153.

*Friedmann Remedy.*—Additional contributions on the Friedmann remedy emphasize previous reports that the remedy has not proved successful either in simple cases of tuberculosis, in surgical cases, or in lupus.—*Therap. Monatsh.*, 1914, vol. 28, p. 630.

*Friedmann Remedy.* (Editorial.)—In the Public Health Service report on the Friedmann remedy the investigators summarize their conclusions in the following succinct statements: "The claim of Dr. F. F. Friedmann to have originated a specific cure for tuberculosis is not substantiated by our investigation. The claim of Dr. F. F. Friedmann that the inoculation of persons and animals with his organisms is without harmful properties is disproved."—*J. Am. M. Assoc.*, 1914, vol. 63, pp. 1690, 1691.

*Lacpinin.* (Kühl, Hugo.)—This article was found to be an emulsion of pine needle oil containing 20 per cent. of the oil of *Abitis sibirica*.—*Südd. Apoth.-Ztg.*, 1914, vol. 54, p. 488.

*Neoheval.*—A combination of hexamethylenetetramine and sulpho-salicylic acid which has been recommended as an antiseptic for the urinary tract.—*Therap. Monatsh.*, 1914, vol. 28, p. 629.

*Orthoform.* (McCleave, T. C.)—Idiosyncrasy to orthoform. The experience reported indicates that it cannot be used with impunity in all persons, even in very small doses.—*J. Am. M. Assoc.*, 1914, vol. 63, p. 1666.

*Parakodin.*—A proprietary name for di-hydro-codeine which has been recommended as an expectorant, a sedative, and a substitute for morphine. Among the secondary effects observed are decrease in appetite, retching and nausea. It is given in doses of from 0.02 to 0.05 Gm.—*Therap. Monatsh.*, 1914, vol. 28, p. 630.

*Phenoval.*—A sedative and hypnotic which has been recommended for the reduction of pain and for nervous patients; also as a narcotic.—*Therap. Monatsh.*, 1914, vol. 28, p. 629.

*Rhodoform.* (Anon.)—A sulphocyanate of hexamethylene-tetramine. It is a white, odorless powder, recommended as an antiseptic for use in the treatment of diseases of the mouth and larynx.—*Chem. and Drug.*, 1914, vol. 85, p. 376.

*Thiophysein.* (Anon.)—A new organic iodine preparation, being an addition-product of ethyl-thio-urea and ethyl iodide. It is easily soluble in water, and is, therefore, a suitable form for the administration of iodine in organic combination.—*Chem. and Drug.*, 1914, vol. 85, p. 376.

## CURRENT LITERATURE.

### DIGITALIS.

The second instalment of Dr. Robert H. Hatcher's two-part paper on digitalis is presented in the October number of the *Druggists Circular*, and, like its precursor, is both interesting and instructive. In it he deals altogether with the pharmacology of this much-experimented-with and much-discussed drug, and closes with an excellent summary which embraces the conclusions arrived at in both papers. An adequate abstract of these papers is almost impossible. Physicians and pharmacists should really read and study the original papers.

The author recapitulates as follows: "Digitalis of the first year's growth is probably as active as that of the second, the cultivated as active as the wild-grown.

"The most active digitalis is not necessarily the best; the best being that which possesses a maximum of therapeutic actions with a minimum of side actions, such as the nauseant and emetic. It is not known at what period digitalis possesses this advantage.

"The drying and storage of digitalis require no exceptional conditions. Like all vegetable drugs, it should be selected carefully, dried properly, and stored so that it will not become mouldy. It will then keep indefinitely.

"Pharmaceutical preparations of digitalis which contain at least 60 per cent. of alcohol in the finished product will keep almost indefinitely under all ordinary conditions of storage, where the containers are kept securely corked and away from sunlight.

"At least two principles—digitoxin (or crystalline digitalin of Nativelle), and true digitalin of Schmiedeberg, or of Kiliani—are obtained from digitalis leaf, and it is possible that a third therapeutically active substance, digitalein, may be so obtained in *fairly* pure form, but not *absolutely* pure.

"It is not absolutely certain that these exist preformed in the leaf.

"There is no digitalis principle or preparation, pharmacopœial or proprietary, which has the advantage of digitalis without certain undesired effects, such as nausea and vomiting. Cumulation, so-called, also pertains to all digitalis principles, as, indeed, it does to all drugs.

"Any pharmacist can obtain digitalis without paying an exorbitant price for it, and he can make a tincture equal to the best, and quite as useful therapeutically as any of the proprietary preparations.

"The tincture represents all of the activities of the leaf; so does the infusion when properly made from leaf in No. 60 powder, and these two preparations have an identical action in corresponding doses.

"The fat-free tincture has no advantages over the official tincture.

"The determination of the digitoxin content of the leaf affords no index of the therapeutic or pharmacologic activity of the drug, but the therapeutic activity may vary in the same direction as the digitoxin.

"No test for digitalis, chemical or biologic, is satisfactory, but the one-hour frog method is probably best suited to the general needs of the pharmacist, and this will probably be admitted to the ninth edition of the United States Pharmacopœia.

"The dose of digitalis cannot be expressed in fixed terms, because it varies widely with the frequency of repetition, the length of time during which it is intended to be taken, and dependent upon whether the patient has recently had similar medication. It is probably safe to say that not more than 45 grains of the leaf or a fluidounce of the tincture should be administered to a patient within a period of one week, and such an amount only under the immediate observation of a trained clinician, and such an amount could not be given safely immediately after medication with digitalis or synergistic drugs." *The Druggists Circular*, October, 1914, p. 607.

J. K. T.

#### NEWS ITEM

Dr. Frederick B. Power will retire from the directorship of the Wellcome Chemical Research Laboratories on the first of December in order to return to the United States where, for family reasons, he will make his future home, at 535 Warren Street, Hudson, New York.

The high character of the research work carried out in these Laboratories under the immediate direction of Dr. Power stands without a parallel in his department of science. It has been truly said that Dr. Power has, during the period of his administration, inaugurated a new era in his field of research in England.

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<sup>1</sup> Compiled by M. G. Smith.

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